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ENDOCRINOLOGY

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ENDOCRINE DYSFUNCTIONS IN RETARDED CHILDREN AND THEIR RESPONSE TO TREATMENT*

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Ten years ago the late Dr. Theodore McGraw, Jr., who was well known to many of the members of this organization, began a study of the endocrine conditions to be found among the children in the special classes of the Detroit schools. He found that twenty per cent of these children showed obvious signs of endocrine disturbance.

METHOD OF STUDY

In the Detroit School System all children who are unable to keep up with regular school work, or those with an intelligence quotient of less than 80 per cent and more than 47 per cent, or a mental age of 5 years, are placed in special classes. All below this level are removed from the regular schools and placed in an institution for the feeble-minded. Our study is limited to the children in the Special Classes.

We started with the conception that any endocrine disturbance of sufficient severity to produce mental retardation must inevitably produce detectable physical signs, such as retarded physical development, by which it should be possible to diagnose the type of glandular disturbance. With this idea in mind, we therefore went to the Special Schools and made an inspection of the children. We observed particularly:

The height and weight in proportion to the age.

The body proportions.

Facies.

Skin, hair and nails.

Stigmata of deviation.

Physical defects such as teeth, tonsils or anemia.

Development of genitalia in the boys.

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 24, 1930.

As a result of this preliminary inspection the children were grouped into three classes: (1) those showing correctable physical defects (chronic infection, anemia, visual defects, malnutrition, etc); (2) those showing definite signs of disturbed development suggestive of endocrine dysfunction; (3) those showing no physical or endocrine abnormalities. The members of the first group were turned over for treatment to the regular Medical Department of the Board of Health. The members of the second group were brought to the Clinic for further study.

In each case one or both of the parents accompanied the child to supply an opportunity for estimating the factor of heredity and to give the birth and infancy history. In each case a trained social worker (Mrs. Reba Talbott Aldrich) visited the home to study the environmental situation and to estimate its influence upon the problem. This contact was extremely valuable in securing the cooperation of the family. In the Clinic the child was thoroughly examined, physical measurements were made, and indicated laboratory studies such as basal metabolism, blood count, Wasserman and x-ray examinations were made.

DIAGNOSIS

The pineal, thymus, sex glands, and suprarenal cortex are probably of greater or less importance in the physical development of the growing child. The pineal, in particular, has been thought to affect mental development. No exact methods of diagnosis of disturbance in the function of these glands have been developed, and attempts at therapeusis have not been successful.

We were left then with the thyroid and pituitary glands as possible causes of defective mental development. In both cases we have available potent extracts capable of producing definite physical effects. In both cases definite physical signs of the glandular deficiency are recognized, making possible the diagnosis of a deficiency.

Our cases of thyroid deficiency have fallen into three groups. (1) In *Clinical Hypothyroidism,* the physical signs of deficiency were present at the time of examination. The subjects showed the cretinoid type of facies, the hypothyroid type of obesity, short, stubby fingers, undergrowth, subnormal temperature, dry skin, tendency to anemia, and low basal metabolism. This type has been adequately described in the literature. (2) In *Congenital Hypothyroidism,* the children at the time of examination may show none of the signs of hypothyroidism as usually recognized. The diagnosis is made on the basis of the family history, presence of goitre in the mother during pregnancy, excessive weight at birth, delay in teething, walking and talking, infantile malnutrition or obesity, and a characteristic failure of physical development which gives a slender, poorly developed skeletal system, tendency to carious teeth, relative overgrowth of the long bones (approaching the eunuchoid type of body build), unstable nervous system and malnutrition. This type gives a normal or high metabolic

rate upon their first test, but the true basal rate is low when obtained upon repeated tests. Their tolerance to thyroid extract is higher than normal. This type corresponds to the "forme fruste" type described in the literature. (3) Instances of *Congenital Goitre* were also noted. The subjects usually give a family history of goitre and show upon examination a thyroid gland which contains palpable nodules or a persistent pyramidal lobe, or both. The gland might be larger or smaller than normal, and soft or hard, depending upon the age of the child (whether in puberty or not) and the amount of iodine that the child had received. This group might also show the characteristics of group one or of group two, or might present a perfectly normal physique except for the abnormal gland.

The pituitary dysfunctions were classified as: (1) *Bilobar Pituitary Deficiency* (Froehlich's Syndrome) and (2) *Anterior Lobe Deficiency.* The characteristic distribution of obesity, genital aplasia and lack of physical energy characteristic of bilobar deficiency have been well described in the literature. Anterior lobe deficiency without posterior lobe involvement is difficult of differentiation from the "forme fruste" type of hypothyroidism. It is characterized by a lack of skeletal and muscular development with retention of the infantile body proportions and genital hypoplasia. The family history gives no evidence of thyroid disturbance and the history of the infancy does not reveal the characteristic physical retardation. The diagnosis was made by exclusion, and it seemed probable to us that many cases in our "Anterior Lobe Deficiency" group were primarily subjects of hypothyroidism, with secondary pituitary failure.

Many cases were found showing evidences of failure of both the thyroid and the pituitary. Cases of achondroplasia, microcephalia, mongolism, cryptorchidism, etc., which may be of endocrine origin, were found and are included under a miscellaneous group.

We were struck by the number of children in whom the parturition history gave evidence of mild birth injury. These children frequently came from parents of good intelligence and good endocrine make-up. In these children the signs of endocrine disturbance were frequently present, but it was felt that the brain injury was probably the more important factor.

TREATMENT

The subjects of thyroid insufficiency were given desiccated thyroid substance in increasing doses until definite evidence of overdosage was obtained. The dose was then reduced to the largest amount the child could tolerate, leaving slight evidence of overdosage such as mild tachycardia on exertion, etc. It was felt that a slight excess was necessary to insure that the full dosage was given and it was believed that this would do no harm if the child were under observation. The dosage was checked at intervals by repeated basal metabolism tests, and in no case was the rate maintained at a level more than five per cent above normal. The subjects of

pituitary insufficiency were given 15 grains of desiccated anterior lobe substance, of a preparation known to have definite potency in that dosage. This quantity was obviously too small in the more severe cases, but because of the expense of the material we could not further increase the dosage.

The children returned to the Clinic each month, where observations were made of their height, weight, pulse rate, general condition, etc. At this time the observations of the parents as to their behavior and physical condition were noted. We received from the teacher in direct charge of the patient a bi-monthly report in which she gave her observations regarding behavior, application, attention span, self-control and interest. The teachers understood that these pupils were being studied in the Clinic but did not know which were receiving treatment and which were being carried as controls. This precaution was taken to eliminate the factor of personal bias. At suitable intervals complete psychological tests were performed which could be compared with one or more of the routine tests performed before the study was undertaken.

MATERIAL AND EXPERIMENTAL DATA

In all, 3585 children were examined; of these 667, or 18.6 per cent showed definite evidence of endocrine disturbance. Of this group, approximately two-thirds were subjects of thyroid deficiency—the other third pituitary deficiency. We found 65 cases of birth injury with developmental disturbances suggesting endocrine dysfunction. There were 85 cases of congenital syphilis. The following tabular analysis indicates some of the more interesting results of the study:

Inspections in schools	3585
Correctable physical defects	1159
Possible endocrine cases	993
No endocrine defect	1433
Cases studied in Clinic	903
Eliminated as non-endocrine	236
Endocrine cases	667
Per cent of total examined	18.6
Number under active treatment	233
Number under control study	151
Basal metabolism tests	450
Other laboratory examinations	200

Four series of data were collected:

1. Progress in school as reported by the individual teachers.
2. Intelligence Quotients (Binet tests).
3. Achievement records (performance on the Pressey and the Stanford scales).
4. Motor and co-ordination tests (performed by L. E. Krumholz).

SCHOOL PROGRESS

Hypothyroidism

Treated		21
	Improved	17 or 80%
	Markedly improved	9 or 43%
	Unimproved	4 or 20%
Controls		11
	Improved	5 or 46%
	Unimproved	4 or 36%
	Definite decline in mark	2 or 18%

Congenital Hypothyroidism (with and without Goitre)

Treated		132
	Improved	101 or 76%
	Unimproved	31 or 24%
Controls		56
	Improved	24 or 43%
	Unimproved	32 or 57%

Pituitary Deficiencies

Treated		39
	Improved	35 or 90%
	Markedly improved	9 or 23%
	Unimproved	4 or 10%
Controls		30
	Improved	17 or 57%
	Unimproved	13 or 43%

Combined Thyroid and Pituitary Deficiency

Treated		21
	Improved	15 or 71%
	Unimproved	6 or 29%
Controls		13
	Improved	6 or 46%
	Unimproved	7 or 54%

Miscellaneous

Treated		20
	Improved	15 or 75%
	Unimproved	5 or 25%
Controls		6
	Improved	2 or 33%
	Unimproved	3 or 50%
	Declined	1 or 17%

An analysis of the school progress in the thyroid deficiency groups shows that in more than one-half of the cases without treatment the tendency is to failure of improvement, or even poorer school work. This tendency is more marked in those cases in which the thyroid deficiency is evident at the time of examination. This finding is corroborated by the intelligence tests. The mentally deficient child with hypothyroidism shows a definite tendency to a falling intelligence quotient, this tendency being most marked if signs of hypothyroidism are still present. Forty-seven per cent of those showing congenital hypothyroidism, and 55 per cent of the actively deficient cases show a falling intelligence quotient. Ten to twenty per cent of both groups, however, show a slowly rising intelligence quotient. No explanation has been found for this fact.

INTELLIGENCE TESTS

Hypothyroidism

Treated—
- Rising I.Q. 14%
- Falling I.Q. 38%
- Same I.Q. 48%

Controls—
- Rising I.Q. 27%
- Falling I.Q. 55%
- Same I.Q. 18%

Congenital Hypothyroidism (with and without Goitre)

Treated—
- Rising I.Q. 14%
- Falling I.Q. 24%
- Same I.Q. 62%

Controls—
- Rising I.Q. 0%
- Falling I.Q. 75%
- Same I.Q. 25%

Pituitary Deficiencies

Treated—
- Rising I.Q. 14%
- Falling I.Q. 22%
- Same I.Q. 64%

Controls—
- Rising I.Q. 10%
- Falling I.Q. 27%
- Same I.Q. 63%

Combined Thyroid and Pituitary Deficiency

Treated—
- Rising I.Q. 0%
- Falling I.Q. 47%
- Same I.Q. 53%

Controls—
- Rising I.Q. 10%
- Falling I.Q. 43%
- Same I.Q. 47%

Miscellaneous

Treated—
- Rising I.Q. 10%
- Falling I.Q. 30%
- Same I.Q. 60%

Controls—
- Rising I.Q. 0%
- Falling I.Q. 20%
- Same I.Q. 80%

The improvement in school work resulting from treatment is confirmed by the results of the Binet tests. In no single case was a marked increase in intelligence noted, but there is a significant tendency to prevent the expected fall in intelligence. Whereas before treatment 55 per cent of the children showed a falling intelligence quotient, but 38 per cent showed a fall during the treatment. Conversely, whereas 45 per cent remained stationary or rose slowly before treatment, 62 per cent held their own or better during treatment. This is particularly significant in view of the fact that many of the children were not treated continuously during the entire period between their tests.

The cases of pituitary insufficiency do not show as marked a tendency to falling intelligence quotients as was noted in the thyroid groups, only 27 per cent registering a fall. No change is noted in the percentages obtained after treatment.

ACHIEVEMENT TESTS

Hypothyroidism

Treated—
Improved 70%
Unimproved 30%
Controls—
Improved 80%
Unimproved 20%

Congenital Hypothyroidism (with and without Goitre)

Treated—
Improved 81%
Unimproved 19%
Controls—
Improved 55%
Unimproved 45%

Pituitary Deficiencies

Treated—
Improved 70%
Unimproved 30%
Controls—
Improved 80%
Unimproved 20%

Miscellaneous

Figures not adequate for analysis.

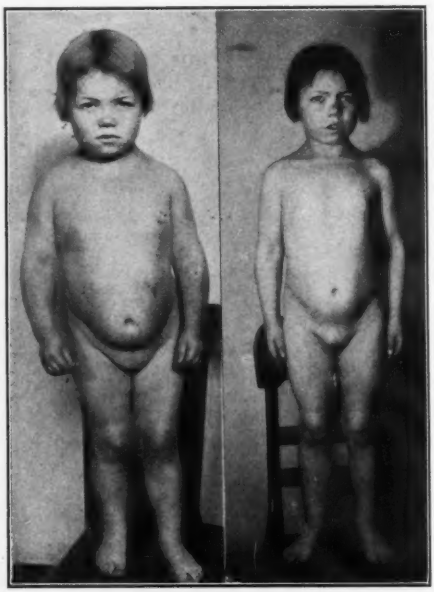
The progress in achievement, as determined by the Stanford tests in the older and by the Pressey tests in the younger children, gives the same results. In the untreated congenital hypothyroid group 55 per cent showed an average gain of 7 months, 33 per cent a loss of 5 months, and 12 per cent no change. During treatment 81 per cent gained an average of 8 months each, and 19 per cent lost or remained the same.

The achievement figures were identically the same in the pituitary group, whether treated or untreated, namely, 70 per cent gain and 30 per cent loss. Here again it will be noted that the pituitary group does not show the tendency to retrogression nor the benefit of treatment recorded in the thyroid groups.

The studies of Mr. Krumholz on the motor functions (speed, steadiness, muscular co-ordination) fail to show any significant trend in any group, whether control or under treatment. This line of investigation is entirely new, and may yield significant information after further study.

A single case history will serve to illustrate in a concrete way the facts presented above. V. M., a girl of 11½, was diagnosed as suffering from hypothyroidism. The family history was devoid of data of endocrine

significance. The birth weight was 8 pounds. In babyhood the patient was lethargetic and extremely constipated. Her first teeth appeared at 13 months; walking and talking began at 13 months. The basal metabolic rate before treatment was —13 per cent; while taking thyroid substance in dosage of 1½ grains the rate was normal.



(A) (B)

FIG. I.

(A)—V. M., age 11 years, 2 months—Before treatment.
(B)—V. M., age 12 years, 2 months—After thyroid treatment. Loss of weight, 2 lbs. Gain in height, 4½ in.—(Courtesy Harper Hospital.)

Her school progress showed well marked improvement. She gained 4 months by the Pressey scale. Her intelligence quotient increased from 55 per cent to 58 per cent. The change in her physical condition can be visualized from accompanying illustration. It will be noted that the physical change from treatment was significantly greater than the mental development.

DISCUSSION

It is our impression that faulty thyroid function in a pregnant woman interferes with the normal development of the central nervous system to a degree depending upon the severity of the thyroid deficiency at different stages in the development of the fetus. This is associated with a disturbance in the development of the fetal thyroid gland, which is demonstrated as a congenital goitre or the picture of congenital hypothyroidism. This thyroid disturbance may undergo spontaneous improvement during the life of the child, with a disappearance of the signs of active hypothyroidism.

Supplying the deficiency of the thyroid hormone enables the poorly developed central nervous system to function at a better rate and more efficiently. It does not, however, repair the damage that has already been done.

Obviously, the earlier the defective secretion is replaced, the less damage will be done, and the more complete will be the clinical improvement. The real solution of the problem lies in the correction of the faulty thyroid function of the pregnant mother.

The children who have already come into the world with this handicap should be given the benefit of adequate thyroid replacement therapy as early as possible, and this treatment should be continued as long as the need for it exists.

It is our hope that this study will stimulate the school authorities and physicians in touch with these problems to the early recognition and proper treatment of these cases.

Our results in pituitary deficiency do not indicate a significant relationship between this condition and mental retardation.

Pituitary treatment, in the dosage supplied, did not significantly alter the intelligence, although there was an improvement in school work, probably due to the stabilizing effect of treatment upon the personality.

SUMMARY AND CONCLUSIONS

Thirty-five hundred children have been studied, with the isolation of 667, or 18.6 per cent, who showed definite signs of endocrine deficiency. Nearly 400 of these children have been followed either as controls or while taking the indicated treatment.

The reports of the individual school teachers, the results of intelligence tests, and of the specific achievement tests give parallel findings. In the thyroid deficiency groups there were noted:

1. A tendency to falling intelligence quotient, decreased aptitude in school and achievement by the special tests.
2. A tendency to the prevention of this fall under treatment.
3. Greater physical than mental improvement under treatment.

In the pituitary deficiency groups there were noted:

1. Less marked tendency to falling intelligence quotient and achievement without treatment.
2. No change in intelligence or achievement as a result of treatment.
3. Improvement in school work unaccompanied by evidence of increased mental development.

These results are entirely in accordance with those reported by Dr. Fox.

We wish to express our gratitude to the entire personnel of the Department of Special Education for their loyal and efficient co-operation in this study; to Parke, Davis & Company, who donated all the Pituitary Extract used in the first year of the study; to Dr. Harry Clark, who performed without recompense over 200 laboratory examinations, and to the Research Committee of the Detroit Board of Education, whose interest and assistance made this work possible.

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PITUITARY HEADACHE*

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This discussion presents five comprehensive case histories in which the clinical picture and treatment course are typical of a series of 60 cases considered under the general category of pituitary headache. The sixty cases are the result of careful selection from patients referred by the gynecological department of St. Luke's Hospital, Chicago, between the years 1921 and 1925 from a clinic which clears about nine hundred patients annually. Our experience would seem to indicate that about 16 out of 1,000 cases of the headaches that constitute so great a problem in the clinical handling of gynecological patients are proper subjects for pituitary therapy.

The usual subjects of pituitary headache are obese women of long-legged, short-waisted build. They are energetic, alert and intelligent. All are subject to such menstrual dyscrasias as amenorrhea, dysmenorrhea, or menorrhagia. The same patient may exhibit all of these conditions at different points in her history, and all show the common history of onset at adolescence, during the first years of married life, or subsequent to childbirth. There is often a family incidence. From patient to patient and in the same patient at different times there is a wide range of variation in symptom complex and treatment response, and the relative constancy of general outline carries no corollary of uniform treatment or fixed response. Each case presents an individual and engrossing therapeutic problem. It is for this reason that the treatment course of our cases is reported with considerable detail and over a much longer period than has been the rule in current literature on the subject.

CASE REPORTS

CASE 1: E. A., female, colored, unmarried, age 20 years, was examined November 12, 1923. She had habitual headache which became progressively worse and was intensified when menses began at the age of 12. These headaches occurred daily since 1921, were exaggerated during menses, confining her to bed. The attacks were four to twelve hours in length, coming on during the day, never at night and never interfering with sleep and usually continued until the patient went to sleep. The headaches, located deep over the left eye were worse on stooping and gradually became generalized and bursting in type, causing a dazed sensation. Excitement induced and intensified the symptoms. There was no sense of anything moving in the head. Nausea, occuring at the climax, brought relief. Aspirin in ten grain dosage was helpful. The headaches were followed by sluggishness and an overpowering sense of fatigue, drowsiness and melancholy. The patient was tired all of the time and neither work nor play could interest her. She was irritable, noises annoyed her and solitude was desired. She was unusually advanced in her school studies, but backward in all

*Read before the Fourteenth Annual Meeting of the Association for the Study of Internal Secretions, Detroit, Michigan, June 23, 1930.

social situations. She avoided men and seemed to understand nothing about sexual desire. Glasses had afforded but slight temporary relief and many other forms of treatment had been quite fruitless.

Physical Examination: The patient appeared serious and unhappy. She was tall and fairly well built, but her legs were disproportionately long and her waist was short. Her figure was rather masculine. The hair on the head was abundant and coarse; some was evident on the upper lip. Pubic hair was masculine in distribution, and extended to the umbilicus. No abnormal hair growth appeared on the arms or legs. The legs were straight and masculine;

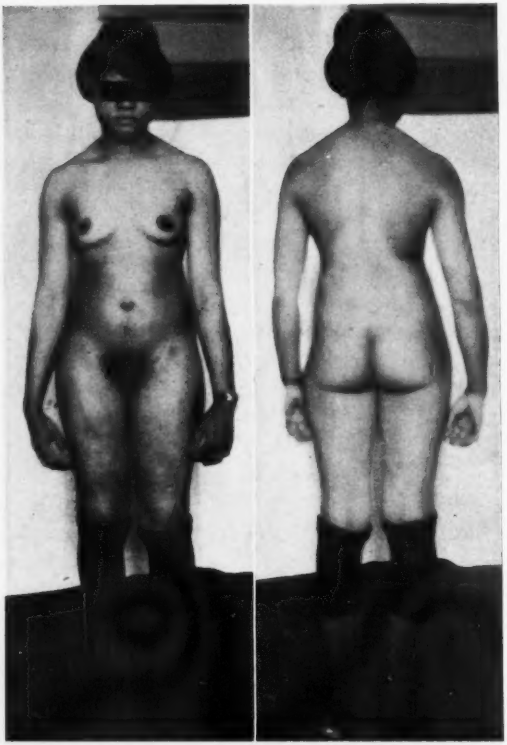

Fig. 1 Fig. 2

Fig. 1. Case I, E. A., showing masculine distribution of pubic hair.
Fig. 2. Case I, E. A., illustrating short waist and long legs typical of altered bone metabolism due to pituitary dysfunction.

the gait and posture were normal. The head was normal in size and the eyes were normally spaced. Refraction had been corrected by glasses. Pressure over supra-orbital region elicited tenderness. Visual fields were not taken. The features were course and the superior maxilla prominent. The upper central incisors were separated. The thyroid was not enlarged and was free from pulsation.

Roentgenogram of the sella showed no evidence of tumor. The space between the anterior and posterior clinoid processes measured about 5 mm.

The chest was well developed. The heart and lungs were normal. The pulse rate was 102, blood pressure 116-68. Blood sugar test was not made. The abdomen and abdominal organs were normal. The external genitalia were infantile. The uterus was small; tubes and ovaries were not palpable.

Treatment: Three subcutaneous injections of Burroughs & Wellcome's infundin (pituitary infundibular extract) in 0.5 cc. doses daily caused the patient to declare she "felt like a different person." She remained free from headaches, while receiving treatment as outlined, but the headaches, never so severe as prior to the administration of pituitary extract, tended to return when medication was interrupted. Whole gland treatment by mouth was substituted when the patient left Chicago.

Medication was interrupted, however, and in February, 1924, the headaches, becoming more severe, compelled her to return to the city. Infundin then administered three times a week and supplemented with whole gland pituitary extract by mouth again controlled the symptoms.

Observations made at four week intervals until June, 1926, showed the patient to be still free from symptoms (Figs. 1 and 2). The patient was last seen a year ago and is entirely free from symptoms.

CASE II: M. R., female, white age 21, was examined at the gynecological clinic in March, 1922, on the suggestion of oculist to find constitutional cause of dysmenorrhea and headaches, which persisted in spite of corrected refraction. Menstruation began at 16 with menorrhagia for five or six months, alternating with amenorrhea for five or six months. Development had been normal during growth period, but weight had increased from 115 to 145 pounds since 1920. Her

Fig. 3. Case II. M. R. The upper teeth exhibit the marked separation frequently found in pituitary types.

appetite was normal and she had never been constipated. Five brothers, four sisters, father and mother were living and well. There was no family history of similar complaints.

The patient had some headache all the time since her early teens. It started in the morning and continued throughout the day without remission. The pain was usually over both eyes, never bursting in type, nor resulting in a dazed sensation. There was not tenderness on deep pressure nor sense of anything moving in the head. The headaches were worse during menstruation, confining the patient to bed. Excitement brought on or intensified the pain and stooping made it worse, as did the consumption of sweets. No nausea nor vomiting occurred at the climax. Coal tar analgesics gave no relief. Her activities were reduced. She experienced fatigue at all times out of all proportion to what she was required to do.

Physical Examination: The patient was short-waisted and long-legged, fairly well built; her weight was about 145 pounds. The skin was normal. Body hair and pubic hair were normal in texture, growth and distribution. Posture and gait were normal. The head was well formed and the hair was abundant. There was no tenderness to pressure on head or face. The temporal arteries were not palpable. Hearing was normal. Eyebrows were normal and there was no puffiness of the lids. The pupils and eye movements were normal. The thyroid was not enlarged. The teeth were clean and in good condition, the upper ones markedly separated. Mouth, fauces and nasal passages showed nothing of interest. The lungs and heart were normal. Pulse rate was 75, and blood pressure was 100-55. The results of the examination of the abdomen were quite negative.

Treatment: On March 13, 1922, administration, by injection, was begun of one ampoule of Burroughs & Wellcome's infundin 0.5 cc. once a day for ten days. When the second ampoule of infundin was administered the headache had disappeared and the patient felt improved in every way. On March 23, when the tenth injection was made, the patient declared she was well and felt like doing her work. On April 19 she experienced a menstrual period, painless and without

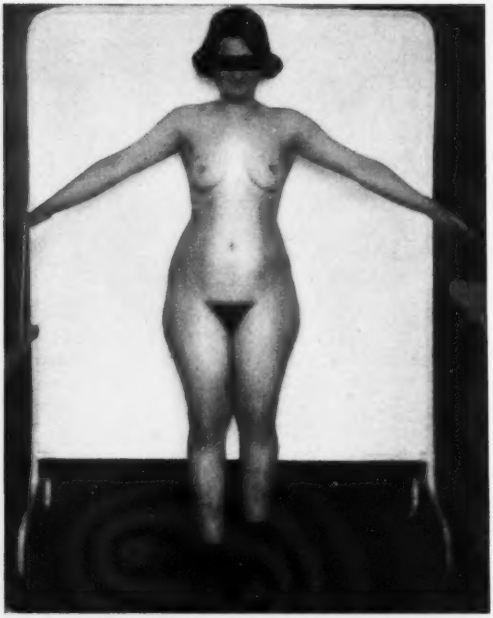

Fig. 4. Case II, M. R., definitely representative of the short-waisted, long-legged individuals who seem predisposed to confusing plurigiandular syndromes.

Fig. 5. Case II, M. R., showing posterior view which illustrates well the disproportion between body and trunk length and a type of adiposity common in pituitary patients.

headache. From March 23 to May 2, the patient received infundin three times a week for one week and then twice a week for one week. On May 2 the patient reported menstruation a week delayed. A headache and severe backache had lasted all night preceding the flow, but vanished when the flow appeared. July 17, 1922, the patient reported having menstruated in June, nine days late, but with no discomfort. She had remained free from headaches, felt well and continued to do her work. Treatment was discontinued.

She reported four times during the ensuing year. She menstruated regularly and remained free from headache up to June, 1926. During this interval the patient married, experienced a normal pregnancy and remained free from symptoms during gestation. Her reason for reporting in June, 1926, was amenorrhea following the pregnancy.

This patient was last heard from in 1928 and she was entirely symptom free. (Figs. 3, 4 and 5.)

CASE III: A. T., female, colored, married, age 21, was examined at the gynecological clinic of St. Luke's Hospital Dispensary, Chicago, November 6, 1921. The complaint was dysmenorrhea for the last year, during which time she had been unable to work, but had gained sixty pounds. She tired easily, felt

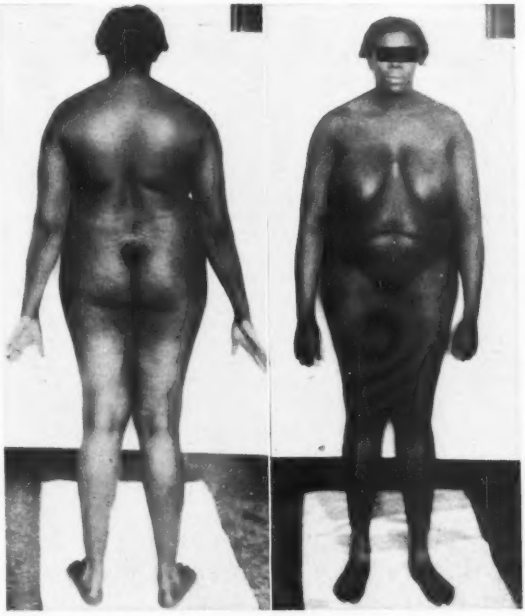

Fig. 6 Fig. 7

Fig. 6. Case III, A. T., exhibiting torso obesity, long legs, and short waist. This patient responded spectacularly to pituitary treatment.

Fig. 7. Case III, A. T., in whom the trunk disproportion connotes sexual repression and cyclic headache of pituitary type.

weak, and was short of breath on slight exertion. She was always thirsty, drank quantities of water, and habitually arose three times at night to urinate. The headaches were frequent, with onset in early morning. They caused a sense of fullness in the head and blurring of vision.

The patient had escaped all diseases of childhood. She attained her growth early, her height at fourteen years being 5 feet 6 inches.

Physical Examination: The patient was tall; the arms and legs were normal, but the trunk was disproportionately large. The head was rather small. The abdomen was fairly firm. Excessive fat about the abdomen hung in folds about the hips and over the mons. There was no supraclavicular padding. The

mammae were somewhat pendulous. There was a marked girdle of obesity extending down to about the middle or third of the femur. There was a transverse scar across the abdomen 18 cm. in length. The body hair was normally distributed and normal in texture. The gait was slightly waddling, but posture was erect and there was no lordosis. The pulse was normal, rate 90. Blood pressure was 140-70. Respiration was normal. Temperature was 99° F.

The head hair was black and kinky; there were no areas of alopecia. There was no tenderness to pressure on the head. The ears were normal. In the fundus of the left eye were seen several old hemorrhages below the disc in conjunction with one large and several small clumps of exudate. The right eye was normal. Face, mouth and teeth showed nothing abnormal. The neck was short, the thyroid normal in size. No pulsation was seen. The chest was well developed with good expansion. The heart and lungs were normal. The abdomen was pendulous; the old healed scar was in good condition. There was no evidence of abnormality in the abdominal organs. Examination showed Skeene's ducts enlarged, with a small cyst underneath the urethra. The uterus, ovaries, and tubes were not palpably diseased, but chronic salpingitis and adhesions were thought probable.

Roentgenogram showed the sella to be completely bridged. The pituitary fossa measured 1.2 cm., the floor somewhat thickened and depressed. The bones of the hands were unusually long, especially the metacarpals. No definite changes, such as rarefaction or osteosclerosis, could be seen in the bones.

Treatment: The routine treatment was instituted with the administration of ten consecutive daily injections of one ampoule of 0.5 cc. Burroughs & Wellcome's infundin, followed by similar injections three times a week for one week; then two times a week for one week; one injection the fourth week, then one in two weeks for a month, followed by an interval without treatment.

After an interval of one month without treatment the patient had lost 38 pounds in weigh on August 13, 1923. Menstruation was regular and free from pain. November 12, 1923, she had gained 11 pounds. The headaches had not returned, but in order to see what influence pituitary therapy would have on the weight, infundin, 0.5 cc., was administered at three day intervals, until five doses had been given. On March 2, 1924, she was still free from headache. February 3, 1926, the headaches had not returned but she had again put on the 38 pounds she had previously lost in weight. Menstruation was regular and free from pain. (Figs 6 and 7.)

CASE IV: P. McC., female, white, married, age 41, was admitted to St. Luke's Hospital, Chicago, April 1, 1923.

Complaint: Headache and dysmenorrhea. The headache, more intense in the morning and almost continuous for the preceding ten years, becoming progressively worse, had been present most of the patient's life. Preceding each menstrual period the symptoms were so intensified as to confine her to bed. Other attacks almost as severe were frequent between periods. They were more severe on alternate days, with almost constant pain and nausea. Frequent vomiting afforded temporary relief.

The patient had one child, whose birth was normal in every way. During her pregnancy in 1920, severe headaches confined her to bed once a week. Headaches were constant while she was in the hospital after the child's birth. The patient's mother, who was subject to similar headaches, had experienced relief during pregnancy and had recovered at the age of 55. Her three sisters had headaches similar in type. The patient's menses began at the age of twelve, were quite painless for two years, regular and of the twenty-eight day type, with a moderate flow for seven days. Since the age of 14 dysmenorrhea had been present. She had leucorrhea for about five days subsequent to menstruation.

The patient said she had pleurisy on the right side at the age of fifteen, and at eighteen had a gastric ulcer. At the present time she experienced occasional pain in the stomach. She seldom drank tea or coffee. She was slightly constipated, used cathartics occasionally. She slept well. About twelve years prior to examination, the patient had begun to take headache medicine. Aspirin, dissolved in strong coffee, helped her most. Her family physician gave her a prescription of acetanilid, which had been taken in 20 grain doses daily for the preceding two years. She said she often took 80 or even 120 grains a day. For three years she had been given hypodermic injections of about one-half grain morphin at menstruation time. This treatment mitigated but did not terminate the attacks.

Physical Examination: The patient, though not acutely ill, looked tired, undernourished, and resembled a chronic sufferer. The skin and scalp were

normal. Vision was corrected for marked hyperopia and astigmatism. The eye muscles, pupils, ears, nose, teeth, ad tongue were normal. The tonsils were small and atrophic; the pharynx was normal; the thyroid was small; there was no cervical adenopathy or rigidity. The breasts were small and atrophic, otherwise normal. The chest wall was thin and poorly muscled. Heart, pulse, and lungs were normal. Blood pressure was 94-68. The superficial vessels were not fibrosed. There was no capillary pulsation, edema, or venous engorgement.

The abdomen was flat, thin-walled, and poorly muscled; the abdominal organs were apparently normal. There was little subcutaneous fat on the extremities, which were otherwise normal. Deep reflexes were normal. There was no curvature of the spine, and no tenderness or rigidity of the back.

Roentgenogram showed normal sella, although the dorsum sellae arched forward nearly to the anterior clinoids. There were no cranial markings that would indicate disease. The blood showed: erythrocytes, 3,820,000; leukocytes, 9,400; hemoglobin, 77 per cent. Specific gravity of the urine was 1.020.

Treatment: One month prior to hospital admission the patient had been given six peptone injections, 1 cc. each, without effect on the headaches. As the patient's mother had been free from headaches during pregnancy, it was thought that the presence of foreign proteins might have been responsible. On admission to the hospital, April 1, 1923, the patient was given daily 0.5 cc. of Burroughs and Wellcome's infundin, intramuscularly. On the eighth day the patient complained of a slight headache. On the ninth day menstruation began with much less than the usual discomfort. The patient was discharged on the seventeenth day.

Medication was continued with the administration of 0.5 cc. ampoules of Burroughs & Wellcome's infundin daily for three days before the onset of menstruation. In November, 1923, despite occasional setbacks, she was still enthusiastic and grateful. A year later she reported having experienced only one headache during the menstrual month and sometimes escaped even that.

She continued taking the pituitary injections a few days before the menstrual period and at other times if she felt a headache coming on. In June, 1926, she was still in good health and she remained free from symptoms in 1929.

CASE V: J. J., female, white, married, age 26. Dispensary patient, January 15, 1923.

Complaint: Palpitation and shortness of breath for ten or twelve years; continuous headache for preceding three weeks. The palpitation, which occurred in paroxysms, often at night, and might be induced by worry or fright at any time, produced a pulse rate of 150 or thereabout. The dyspnoea on exertion was worse after an attack of influenza, and had become progressively worse during a pregnancy, which terminated in November, 1922, with the birth of a child. She had been "nervous" for thirteen years, with the habit of biting lips and nails; she was readily excited and irritated. Her husband and baby "get on her nerves" and often, especially at menstrual periods, she could not bear to have them around.

During a previous pregnancy she gained fifteen pounds. Her weight then remained at 196 pounds until the present pregnancy. Headaches, migrainous in type, a week in duration, with remissions of seven days, were coincident with weight increase. Regular menstruation, re-established three months after the baby was born, was without pain but was ushered in with unusually severe headaches, irritability and severe exhaustion. Sexual life was fairly normal for the first nine months of the married life, later on was "just endured."

Treatment: Beginning November 23, 1924, 0.5 cc. of Burroughs & Wellcome's infundin was given hypodermically every day for ten days, followed in the usual manner with one injection three times a week for one week, twice a week for one week, once a week for one week, and then once in two weeks for a month, followed by an interval free of treatment. The headache disappeared after the initial injection and for the first time since the birth of her baby she was able to take long walks in the open air, and felt like doing her work. Headaches recurred, but in much less severe form, when she menstruated a month after treatment was begun, but when headache was present a single injection of pituitrin brought relief at once.

A few months later the patient was put on a diet of 1,400 calories and within a month she experienced a weight loss of 13 pounds. She felt better, slept better, was not so short of breath, and did not "feel all dragged out." The diet was then reduced to 1,100 calories but soon she felt weak and returned to 1,500 calories. She had no headache for three weeks, but experienced one attack of tachycardia. Thyroid was then given by mouth for the first time, ½ grain

each morning for a week. The menses came on during this week without a headache. There was a further weight reduction of six pounds. The thyroid dosage was then raised to 1 grain daily. The pulse rate was 80. The patient felt greatly improved and menstruated for three consecutive times without a headache. However, after four months of freedom from headaches, she began to experience nightly attacks of palpitation, and this was an annoying complication for about two months, when she began to have alternate attacks of palpitation and headache preceding the menstrual period. During the attacks of palpitation thyroid was discontinued, as it was thought that the thyroid medication was a possible cause of bringing on the tachycardia.

The palpitation continued for a few months when it suddenly disappeared. Thyroid was again instituted and the palpitation did not return.

Over a period of six months treatment the patient had lost 54 pounds in weight. She remained free from headache for two years. For one year, she continued to receive the pituitary extract injections daily for three days before onset of menstrual period. The last year she had received no medication and had remained free from symptoms.

The patient was free from symptoms when last heard from in 1929.

SUMMARY

1. Pituitary headache occurs only in women. We have never observed in men any type of headache that is in the least amenable to pituitary therapy.

2. Pituitary extract, by injection, is the only effectual remedy. Pituitrin, by mouth alone, has failed to give satisfactory results. Pluriglandular therapy is of no avail. The use of thyroid extract is contraindicated.

3. The characteristic menstrual dyscrasias associated with pituitary headache are subject to incidental correction by means of pituitary therapy administered for relief of headache. They require no direct attention.

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HUMORAL MECHANISMS CONCERNED IN OVULATION IN THE RABBIT

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The female of most mammalian species exhibits a definitely regular rhythm in ovarian activity in which ovulation is an incident. It has long been accepted that the cyclic variations in the ovary and in the accessory reproductive organs are effected by some hormonal influences, although the identity of the hormones was not known. Even today one could not say definitely what these hormones are. Yet, as a result of the stimulating researches of Smith and Engle (19), and Zondek and Ascheim (21), as well as the works which these researches provoked, it has become increasingly apparent that one must consider the anterior lobe of the hypophysis among those elemental forces that pulse the rhythms in the generative system of the female.

There are some animals, however, that do not exhibit rhythmic ovarian activity; of these the rabbit is one. In the mature female of this species there is no periodic recurrence of heat, and similarly, no such recurrence of those ovarian changes which culminate in ovulation. The rabbit does not ovulate spontaneously, but only after coitus. At any time of the year, in an entirely unpredictable manner, the follicles in the ovary of an unmated female may develop to maturity. In such state they remain, apparently unchanged until the act of coitus releases those changes which result in ovulation some ten hours later. Because of this state of affairs, it was thought that the process of ovulation in the rabbit differed markedly from that in other animals. Thus, Heape (9) considered it extremely probable, "on the basis of observations made on the nerves of the ovary," that the discharge of the ova was effected by the stimulation of some erectile tissue in the ovary. Similarly, Marshall (14) considered the phenomenon reflex in nature. In his opinion the evidence pointed to the conclusion that "the discharge of the follicles occurs in response to a stimulus conveyed to the ovary by its nerves."

Recent studies have made such views untenable.

EVIDENCE FOR THE PRESENCE OF A HUMORAL MECHANISM FOR OVULATION IN THE RABBIT

In 1929 a series of ovarian autotransplantations was performed on rabbits (Friedman, 5). In a single operation both ovaries were completely excised, and a few small pieces of ovarian tissue were placed in a canal in the rectus abdominis muscle. Shortly afterwards repeated attempts were made to mate these females. From five to seventeen weeks after the

operation thirteen of the fifteen females so prepared accepted coitus. At autopsy, 48 hours after coitus, large, blood-filled vesicles were found in the rectus muscle at the site of the transplant. Upon histological examination these blood-filled vesicles (Fig. 1) proved to be corpora hemorrhagica with

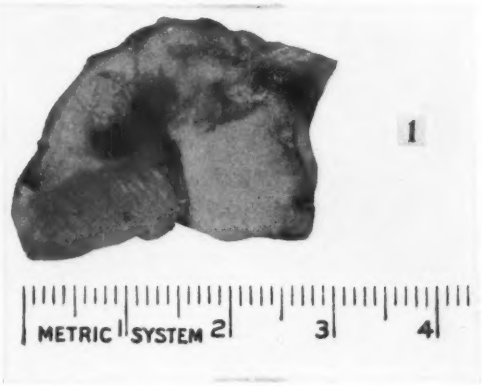

Fig. 1. Photograph of rectus muscle showing two corpora hemorrhagica protruding from the transplant.

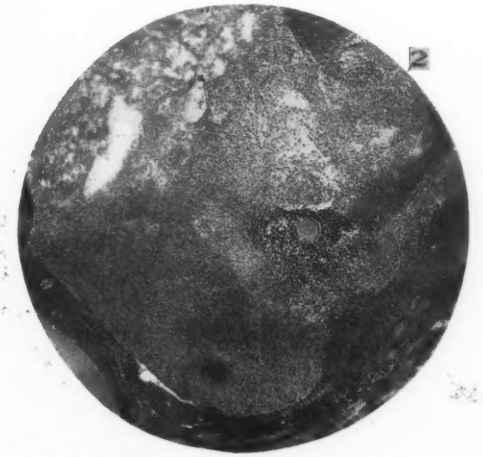

Fig. 2. Microphotograph of a section through a corpus hemorrhagicum showing the retained ovum.

retained ova (Fig. 2).* In addition to these corpora hemorrhagica, genuine fresh corpora lutea were found in the transplants in two instances. In one animal which showed such corpus luteum (Fig. 3) the recently discharged egg was found in the tissue about the transplant (Fig. 4). On the basis of such evidence it was concluded that ovulation in the rabbit may occur without the participation of the ovarian nerves.

*The figures in this paper have been previously published as illustrations of articles in the American Journal of Physiology.

Since these results were published I have encountered an earlier experiment which lends support to the results I obtained. In 1900 Knauer (12) performed a large number of experiments on dogs, cats and rabbits to

Fig. 3. Microphotograph of a section through the equator of a corpus luteum in the transplant of an animal 20 hours after coitus. Transplantation performed five weeks previously.

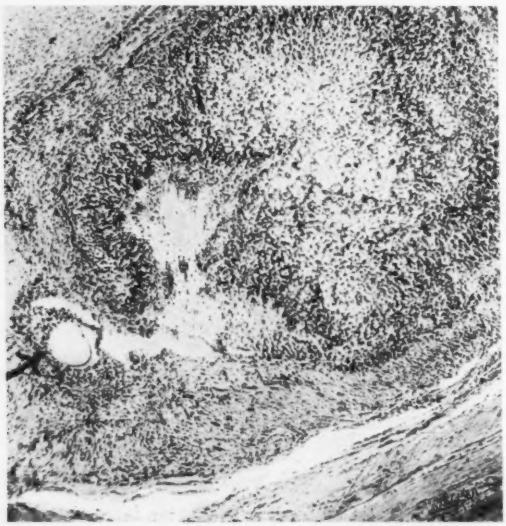

Fig. 4. Microphotograph of a section through the same corpus luteum ventral to the equator showing the recently discharged ovum (arrow).

demonstrate the adequacy of ovarian transplants in preventing uterine atrophy. Among the experiments on rabbits is a record of a successful ovarian transplant to the broad ligament. In a subsequent operation on

the same animal to inspect the condition of the uterus, the infundibulum of the fallopian tube was approximated to the ovarian graft and anchored there. Upon recovery from this operation the female was placed with a male. A month later she dropped a litter of normal young to bear testimony that ovulation may occur in ovarian transplants.

Yet, granting that some humoral change, or changes, are responsible for ovulation in the rabbit as well as in animals which ovulate spontaneously, one immediately asks as to the nature of these changes. Fortunately, there appeared almost simultaneously three reports which permit the presentation of a plausible hypothesis. Fee and Parkes (4) published some experiments in 1929 in which ovulation in the rabbit was prevented by an acute hypophysectomy within one hour after coitus. A similar operation performed later than one hour post coitum failed to prevent ovulation. Shortly after the experiments of Fee and Parkes, ovulation in the rabbit was produced by a single intravenous injection of an extract of the anterior lobe of the pituitary (Bellerby, 1), and by the single intravenous injection of whole urine from a pregnant woman (Friedman, 6). In these experiments the interval between the time of injection and ovulation was about ten hours, a time interval equal to that between coitus and ovulation. The work of Bellerby and of Friedman has since been confirmed by Jares, in Corner's laboratory (11), and by Hill and Parkes (10).

From these several researches it seems quite probable that in the rabbit the act of coitus stimulates the pituitary gland to discharge some hormone (or hormones) which, acting on the ripe follicles in the ovary, produces those changes which result in ovulation.

DISCUSSION

Regardless of the plausibility of the hypothesis that has just been presented, it is necessary to call attention to the objections that have been raised against some of the evidence upon which the hypothesis rests. From more than one source has come the caution against the assumption that the substances in the urine of pregnant women, and in the extracts prepared from the hypophysis are really anterior lobe hormones. Recently, Hill and Parkes (10) were unable to obtain ovulation in acutely hypophysectomized rabbits by the injection of extracts from the urine of pregnancy. They say, "These results throw some doubt on the gonad-stimulating substance obtainable from urine of pregnancy, and emphasize the desirability of avoiding the current fallacy of testing such extracts on animals with their own hypophysis intact." This criticism of Hill and Parkes is entirely justified, insofar as most biological tests of such extracts have been performed on animals in which the pituitary had not been removed. Yet, the experimental evidence which prompted this criticism does not remove the possibility that the gonad-stimulating material in the urine of pregnancy is an anterior lobe hormone. In the first place the experiments of Hill and Parkes were performed on decerebrate rabbits. Secondly, extracts of urine, not whole, untreated urine, were used for injection.

When one considers the possibility that an extraction process might result in a product more toxic than the urine itself, it will certainly be conceded that it would be better to examine the material in question by testing it on animals in better condition than are most decerebrate rabbits.

The criticism offered by Hill and Parkes, however, is not the only one which would raise a question as to the identity of the potent material in the urine of pregnancy and in extracts of the pituitary. Engle calls attention to the fact that the results obtained by the subcutaneous injection of whole pregnant urine in the immature mouse or rat are not identical with the results obtained by the daily implantation of fresh pituitaries. While the implantation of the fresh glands leads to the maturation of follicles and ovulation, the subcutaneous injection of whole urine leads to the luteinization of follicles without ovulation. From such data, Engle (2)

Fig. 5. Microphotograph of a section through a corpus luteum in the ovary of a rabbit 20 hours after a single intravenous injection of whole urine from a pregnant woman (×57).

infers that, "If both the gonad-stimulating factor and the lutein producing factor are ascribed to the anterior lobe, then it must be assumed that there are two factors which act on the ovary, or that the same factor acts in a different manner in combination with the urine and as prepared in certain extracts, than when given in the fresh transplant." In a later paper (3) Engle voices the opinion that "It is difficult to consider the two types of response as being due to the same factor from the anterior lobe."

The evidence cited by Engle is not disputed. Nevertheless, his is not the only possible inference, as is attested by the results obtained by Bellerby and by Friedman. In the experiments of Bellerby (1) the single, intravenous injection of a hypophyseal extract provoked ovulation in the injected rabbits, although the subcutaneous injection of the same extract

resulted in the luteinization of follicles with retained ova. Similarly, in the experiments of Friedman (6), the single intravenous injection of urine from a pregnant woman was followed by ovulation in the injected rabbits (Fig. 5 and 6), while the repeated intraperitoneal injections of similar

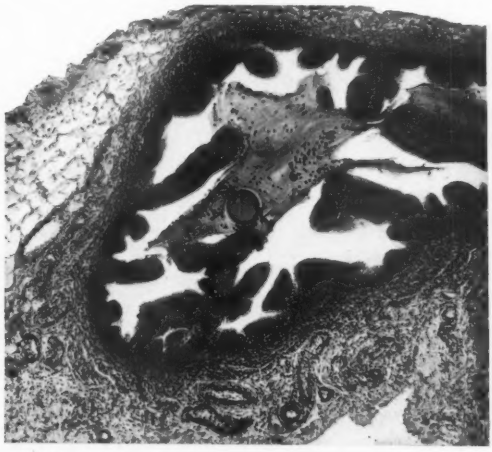

Fig. 6. Microphotograph of a section through the fallopian tube of the same rabbit showing one of the discharged eggs.

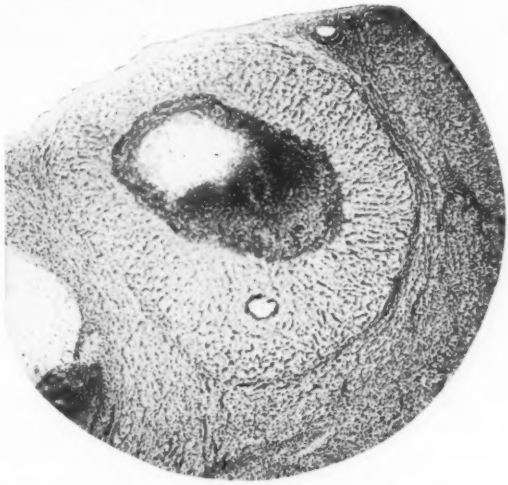

Fig. 7. Microphotograph (×43) of a section through a partially luteinized corpus hemorrhagicum resulting from the repeated intraperitoneal injections of urine of pregnancy. The retained, degenerating ovum can be seen toward the base of the corpus hemorrhagicum.

urine produced the luteinization of follicles with retained ova (Fig. 7). Clearly, then, the mode of administration and the dosage must be considered as factors which are possibly responsible for variations in the response of the ovaries to the injection of any material.

Nor are these the only factors that must be given consideration. In the experience of Zondek the response of the immature mouse ovary to the injection of whole urine is highly variable, even when the age of the mice used is kept relatively constant, and the amount of urine injected and the route of administration kept uniform. It is just because of this variability in response that five mice are prescribed for the performance of each test for pregnancy by the Zondek-Ascheim method. Indeed in a given mouse the reaction of one ovary may be positive, while the response of the ovary on the opposite side is negative (20). In the rabbit, also, there are some variations in the ovarian response to a standard procedure which throw some interesting light on the question. During the course of over a hundred experiments for the diagnosis of early pregnancies (7), I most frequently noticed the formation of partially luteinized corpora hemorrhagica (with retained ova) in the rabbit ovaries. In some instances, however, fresh corpora lutea were seen, identical in every respect with the very early corpora lutea resulting from ovulation. Inasmuch as the route of injection in these experiments was constant, and the dosage of urine constant, we are left with only two variables to explain the variations in the response; namely, the concentration of the active substance in the urine samples, and the condition of the ovarian follicles at the time of the injections.

More striking than such results, however, was the finding in one of the animals used in the series for the diagnosis of pregnancy. In this animal one ovary contained several partially luteinized corpora hemorrhagica. In the other ovary were as many genuine, early corpora lutea. It is unfortunate that careful microscopic examination of the fallopian tubes of this rabbit was not carried out to prove without possible doubt that ovulation occurred in one ovary but not in the other. Nevertheless, the genuine, fresh corpora lutea in the one ovary seem sufficiently strong evidence for the probability of ovulation on one side, while the partially luteinized corpora hemorrhagica of the other ovary afford unquestionable evidence of the failure of ovulation on the other side. Rather than assume that one hormone acted exclusively on one ovary and that another hormone acted exclusively on the ovary of the opposite side, I should prefer to consider the possibility that purely local conditions in each ovary governed the response to the same substance or substances in the circulating blood.

Such variations in ovarian response to stimuli are found not only in the animal subjected to urine injections, but also in the normal animal. In the cyclic ovulation in rats it is not every one of a batch of apparently ripe follicles that responds normally to the ovulation-stimulating mechanism. Although ovulation occurs from most follicles, ovulation may not occur in others, the follicles forming corpora lutea with retained eggs (13). In the rabbit, too, there are instances in which the follicles do not all respond typically to the normal stimulus for ovulation. Not infrequently one finds, 24 to 48 hours after coitus, one or two corpora hemorrhagica

with retained ova in an ovary which contains several perfectly normal, fresh corpora lutea (8).

In view of these several types of evidence indicating that the ovarian response is determined not alone by the nature of the stimulus supplied, it seems the more cautious course to respect the possibility that the gonad-stimulating material in the urine of pregnant women may be an anterior lobe hormone. Recently, a new bit of evidence has been presented which supports this possibility. If one records the spontaneous contractions from the uterine fistula of an unanesthetized rabbit in heat, one usually sees fairly vigorous contractions. Within five to seven hours after coitus a similar recording will disclose only feeble activity if any at all. Before the tenth hour post coitum the uterine activity as recorded from the fistula is usually completely inhibited (15). It is important to note that this effect on the uterus is manifest before ovulation has occurred, and therefore cannot be a consequence of ovulation. With this in mind, it is particularly interesting to note that the decrease in uterine activity which follows the act of coitus can be exactly duplicated by the single intravenous injection of urine from a pregnant woman (16). Indeed, if one were to examine a series of tracings obtained over a ten-hour period from uterine fistulae in rabbits which had just copulated, and from the uterine fistulae of rabbits that had received the injection of an active urine, one could not possibly tell which was which. Just how the substance in the urine affects the uterine activity is not known; perhaps, through a direct action on the uterine musculature; perhaps, indirectly, through the ovaries or through some other intermediary. Nor is the identity of the inhibiting substance known. We are certain it is not folliculin, inasmuch as folliculin in the quantities contained in 5 cc. of urine from a pregnant woman has either no effect at all on the uterine activity (17) or a slight stimulating effect.*

I believe it is probable that the ovulation inducing substance and the uterine inhibiting substance are the same. At present there is at hand no satisfactory evidence which would permit a more definite statement than that. Furthermore, we should hardly be justified in regarding the substances present in urine of pregnancy, and in hypophyseal extracts, as anterior lobe hormones. Although the evidence which prompted such criticisms as those of Engle, and of Hill and Parkes, is inadequate to exclude possibility, the evidence which can be marshalled for the identification of the substances in question as anterior lobe hormones is almost equally inadequate.

SUMMARY

1. It has been demonstrated that some humoral mechanism is concerned in ovulation in the rabbit just as it is in animals which ovulate spontaneously.

*We have not concerned ourselves with any other substances which might possibly be derived from the pituitary and which might affect uterine activity, such as the oxytocic substances, inasmuch as there is not available evidence indicating their presence in the urine of pregnancy. Moreover, such substances have a fleeting, stimulating effect on uterine activity (18).

2. Ovulation in the unmated rabbit can be provoked by a single intravenous injection of an extract of the hypophysis, as shown by Bellerby, or by the single intravenous injection of whole urine from a pregnant woman.

3. The subcutaneous injection of such extract, or the repeated intraperitoneal or repeated intravenous injections of whole urine from a pregnant woman usually result in luteinization of follicles without ovulation.

4. The response of the ovary to the normal stimulus for ovulation, as well as to the substances obtained from the extraction of the anterior lobe and to the urine of pregnancy, is dependent not only upon the condition of the follicles at the time the stimulus is applied, but also upon the manner of administration of the potent substances constituting the stimulus, and upon the dosage of these substances. Therefore it seems unwise to draw any conclusions as to the nature of these potent substances, or as to the existence of one, or two, or more substances merely on the basis of the type of ovarian response elicited until the variable factors we have mentioned have been adequately and carefully controlled.

5. Finally, it appears very suggestive that the response of the rabbit ovary, and of the rabbit uterus, to those changes which are the consequence of coitus can be so exactly duplicated by the single intravenous injection of urine from a pregnant woman.

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THE ROLE OF THE POSTERIOR PITUITARY GLAND IN THE EXPERIMENTAL PRODUCTION OF ARTERIOSCLEROSIS*

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Periodically sufficient data accumulate to permit us to view certain unsolved problems from a new angle. Such a condition, I believe, now exists in the problem of arteriosclerosis. In this paper will be shown that the posterior pituitary gland secretion is an important factor in the experimental production of arteriosclerosis.

Experimental production of arteriosclerosis in rabbits has been accomplished by several workers using various sorts of diets high in fats or fat-like substances to produce these changes.

The relationship between the pituitary gland and carbohydrate and fat metabolism suggested that the pituitary secretion might be concerned in arteriosclerosis. Likewise the pressor effect of posterior lobe extract on the blood vessel wall was another consideration that suggested the use of this substance.

At present it is recognized that fat metabolism is linked with the production of arteriosclerosis. That an intimate relation exists between cholesterol and atheromatous changes in the blood vessels has been known for some time.

The importance of the suprarenal cortex in cholesterol metabolism is well known. Suprarenal cortex hyperplasia in arteriosclerosis, hypertension, and nephritis has been described by many writers. Goldzieher (1) says, "The intimate correlation between lipoid metabolism, adrenal cortex, and atherosclerosis is striking, although its mechanism is far from being clear. The cholesterol disturbance in atherosclerosis and its relationship to the changes of the adrenals has closed the ring of evidence which seems to prove that adrenal hyperfunction is among the most important factors in atherosclerosis, which we believe is but one particular manifestation of genuine hypertension."

A consideration of the correlation between the pituitary and suprarenal glands is therefore desirable. In other articles (2) it was shown that the state of the pituitary is reflected or mirrored in the suprarenal cortex. This relationship of the pituitary and suprarenal cortex is one of the most definite in endocrinology. Aplastic states of the pituitary are accompanied by aplasia of the suprarenal cortex and conversely hyperplasia of the pituitary results in hyperplasia of the suprarenal cortex.

We were led to use posterior lobe extract by the work of Krogh (3). He concluded from his experiments that the posterior lobe secretes a sub-

*This paper is based upon work carried out with the assistance of Eugene A. Osius, M.D. The details have been published by the joint authors elsewhere. Sincere appreciation is expressed to the technical staff of Harper Hospital laboratory for their enthusiastic cooperation.

stance in low concentration which maintains capillary tone. Its pharmacologic pressor effect on the (mesodermal) blood vessels is well known and was further argument for using this substance in the experiments.

EXPERIMENTAL ANIMALS

Observations were made upon four groups of rabbits. A control group consisted of 5 normal rabbits on a normal laboratory diet of hay, lettuce, vegetables, etc.

Group A consisted of 5 rabbits which were fed on a normal laboratory diet with the addition daily of 12 cc. of cottonseed oil and 4 gms. of anhydrous lanolin for each rabbit. This is the diet used by Shapiro (4); it contains a large amount of cholesterol.

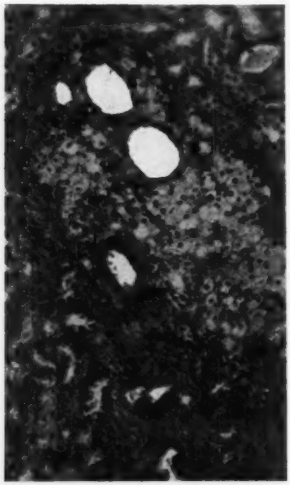

Fig. 1. Lipoidosis of Interstitial Tissue of Kidney. High Fat Diet plus Pituitrin.

Group B consisted of 10 rabbits which were placed on the same high fat diet as Group A and in addition received 1 cc. of obstetrical posterior lobe extract (Parke-Davis & Co. commercial pituitrin)* injected either subcutaneously or intraperitoneally.

Group C consisted of 10 rabbits that were placed on a normal laboratory diet the same as the control group and in addition received daily 1 cc. of posterior lobe extract injected subcutaneously or intraperitoneally.

Blood cholesterol estimations, using Sackett's modification of Bloor's method (5), were made every ten days and the weights of the animals were taken at the same interval. The lanolin and cottonseed oil were heated and then poured onto the food. All animals were kept under the same conditions in the laboratory.

*The pituitrin used in the experiments was kindly supplied by the Biological Department of Parke-Davis & Co. It was conveniently put up for us in specially prepared 30 cc. vials.

Except for a few areas of local irritation, the animals tolerated the injections of posterior lobe extract very well.

The first week we gave the injections twice a day and, following this, once a day over a period of one hundred days so that the average amount injected was 107 cc. of posterior lobe extract.

We began sacrificing the animals on the hundredth day of the experiment, by injecting air into the auricular vein. Immediate autopsy was performed. Only some of the more important details will be given.

The fur of the animals on the high fat diet as well as those on the high fat diet and posterior lobe injections, became and remained more ruffled and shaggy than normal, the appearance of the animals' coats bearing a strong resemblance to that of the guinea pig during anaphylactic shock.

EFFECTS IN THE SUPRARENAL GLANDS

The actual suprarenal weights as well as the ratios of suprarenal to body weights are presented in tabular form.

Average Suprarenal Weights

Control Group	(Normal Diet)	278 mgms.
Group C.	(Normal diet plus posterior lobe injections)	415 mgms.
Group A.	(High fat diet only)	435 mgms.
Group B.	(High fat diet plus posterior lobe injections	639 mgms.

Suprarenal weight—Body weight Indexes
(Mgm.: 100 gm.)

Control Group		Average index 22.9
Group C.	(Normal Diet plus Injections)	Average index 27.5
Group A.	(High Fat Diet)	Average index 28.5
Group B.	(High Fat Diet plus Injections)	Average index 54.8

It is interesting to note in relation to the problem of arteriosclerosis that the suprarenal weights of the injected groups are much higher than the non-injected groups. Microscopic examination of the suprarenals showed that increase was confined to the cortex, the medulla being normal.

EFFECTS IN THE AORTA

Control Group: Not one of the control group showed the least suggestion of arteriosclerosis.

Group A: (High Fat Diet). Four of the five aortas showed macroscopic arteriosclerotic changes. Illustrative of this is the following as reported by the pathologist, Dr. Plinn F. Morse: The "aorta shows a few pin-point whitish plaques and over the surface are scattered irregular shaped areas of whitish density producing a somewhat mottled appearance. There is some increase of fat beneath the intima at the exits of the vessels." These observations confirm the work of others that the high fat diet alone produces arteriosclerosis.

Group B on a high fat diet plus injections of posterior lobe extract showed the most intense lesions of all. Eight of the ten surviving animals showed arteriosclerosis. The following report by the pathologist illustrates

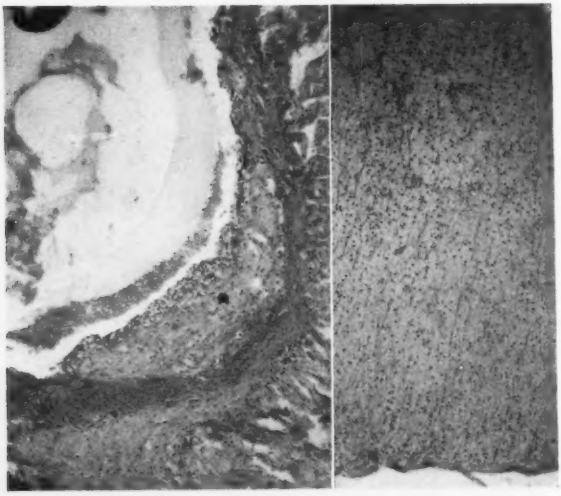

Fig. 2 Fig. 3

Fig. 2. Coronary Sclerosis. High Fat Diet plus Pituitrin.
Fig. 3. High Fat Diet plus Pituitrin. Showing Suprarenal Cortex Hypertrophy, Lipoidosis and Exhaustion Appearance of Cells.

the intensity of the lesions: There are "extensive linear and nodular atheromata distributed densely throughout the course of the aorta, as well as plaques varying in size from several mm. to pin point around the inter-

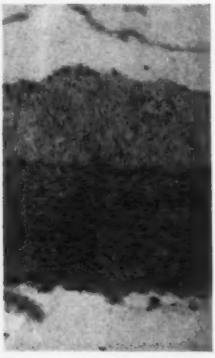

Fig. 4. Abdom. Aorta. Rabbit on High Fat Diet plus Pituitrin. Showing Arteriosclerosis.

costal arteries." Not all of this group showed such extensive involvement as that described, but unquestionably this group showed the most extensive lesions.

Group C on a normal diet and posterior lobe extract injections showed the following results: Six of the ten aortas were reported as macroscopically normal; four showed changes suggestive of early arteriosclerosis. These changes were not comparable to those in Group A on high fat diet alone. The pathologist described one of the aortas as "essentially a normal vessel except for diffuse indistinct whitish areas at the cephalic end." The average suprarenal weight of this group C was almost as much as the high fat group, being only 20 mgm. less than the latter. The average suprarenal index was only 1 less than the average of the high fat group.

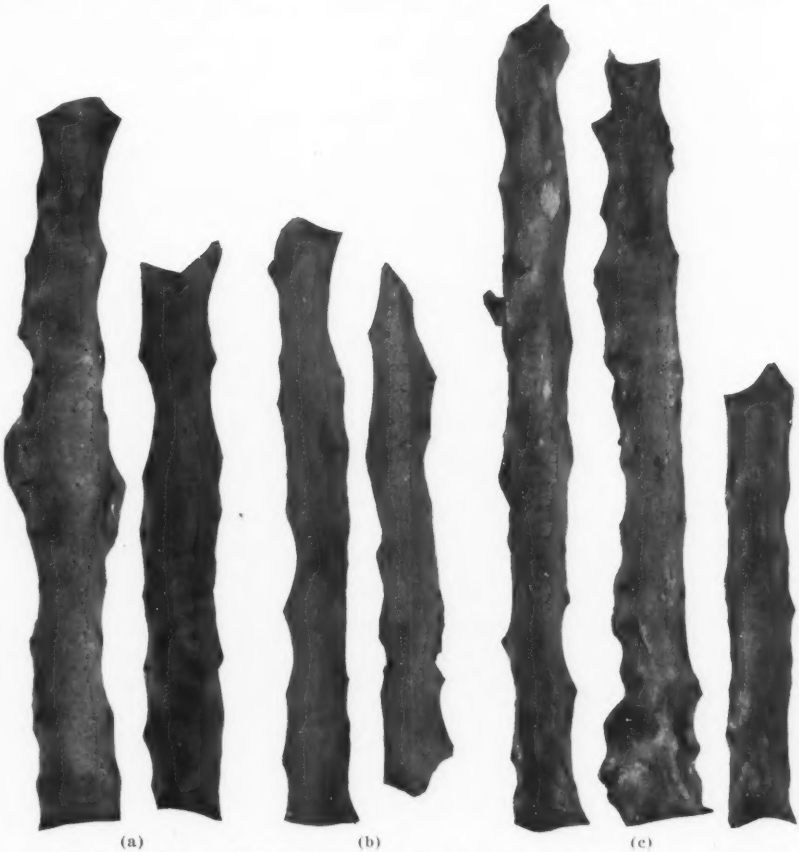

Fig. 5. (a) Aortas—High Fat Diet Only. (b) Normal Diet plus Posterior Lobe Extract. (c) High Fat Diet plus Pituitrin.

DISCUSSION

In previous articles (2) we have discussed at length the special relationship of the pituitary to those tissues that arise from the mesoderm. The importance of suprarenal cortex hypertrophy in arteriosclerosis, hypertension, and nephritis makes the suprarenal cortex hypertrophy found in

our injected animals of great significance. By the injection of posterior lobe extract alone, without the influence of diet, we are able to produce a suprarenal cortex hypertrophy, an important link in the chain of arteriosclerosis. The embryohormonic relations of the pituitary to mesodermal tissues furnishes the most reasonable conception of the problem.

SUMMARY

(1) Two groups of ten rabbits each were treated with high fat diet or this with pituitrin injections. Two control groups were fed on normal diet and of these one received pituitrin.

(2) Either fat diet alone or pituitrin injections alone caused hypertrophy of the suprarenal cortex. The two in combination caused a notably greater hypertrophy.

(3) Similarly marked arteriosclerotic changes were noted in the aortas of those rabbits receiving combined fat and pituitrin treatment. Lesser degrees of involvement were noted following either treatment singly.

(4) The embryohormonic relation of the pituitary to mesodermal tissues is offered as a reasonable explanation of the relationships shown.

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THE EFFECT OF CHOLECYSTOKININ ON THE HUMAN GALL BLADDER

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In previous studies (1) (2) (3) (4) the following observations have been made: (a) The upper intestinal mucosa can be extracted so as to yield a product which on intravenous injection causes the gall bladder of the dog and cat to contract and evacuate. (b) The contraction of the gall bladder in dogs has been observed visually and moving pictures have been made. (c) The contraction and evacuation of the gall bladder is due to the effect of a specific substance, since it has been shown not to be due to a change in liver volume, a change in blood pressure, or contraction of adjacent structures, and since the active principle can be extracted only from the intestinal and gastric mucosa. (d) In cross-circulation experiments it has been shown that acid placed into the duodenum of one animal not only caused the gall bladder of that animal to contract, but about eight minutes later caused the gall bladder of the second animal to contract. These observations lead us to conclude that a hormone mechanism was concerned in gall bladder contraction and evacuation.

It was thought important to extend these observations to the human being. Before doing so it was necessary to demonstrate the existence of cholecystokinin in the intestinal mucosa of man, which has been done by Drewyer and Ivy (5) and to purify the active principle so that it could be injected intravenously into man without producing disturbances.

THE PREPARATION OF A CHOLECYSTOKININ CONCENTRATE

In a previous communication, Ivy, Kloster, Lueth and Drewyer (3) reported a method for the preparation of cholecystokinin from the upper intestinal mucosa of the hog. The product was active in the dog in from 5 to 10 mgm. doses. The precipitation of cholecystokinin by trichloracetic acid and its solubility properties in alcohol has been confirmed by Still (6).

We desire to report now an additional procedure which when applied to the above preparation uniformly yields a product active in approximately 3 mgm. doses in the dog—the product which we have used to study the effect of cholecystokinin on the human gall bladder.

Methods of Preparation: The "1860" Method: (a) One gram of "A pH 1802" powder (3) is dissolved in 30 cc. of water. (b) To this is added 70 cc. of absolute ethyl alcohol. The resulting solution is occasion-

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ally cloudy. (c) To this solution is added from one to two volumes of absolute acetone (aldehyde free). The amount of acetone to be added varies with different batches of "A pH 1802" powder. One volume is first added and then mixed thoroughly by shaking. If a flocculent precipitate does not result, or if the precipitate formed goes into solution on shaking, a full or one-half volume more of acetone is added. The precipitate is impurity and only a small amount of cholecystokinin is lost when two volumes of acetone are added. This impurity amounts to from one-half to two-thirds of the original weight of the "A pH 1802" powder. (d) The precipitate is removed by centrifugalizing. (e) To the filtrate is added five volumes of anhydrous ether (aldehyde free). A precipitate results which is allowed to form for one or two hours. The precipitate is collected by spinning and contains the activity. It is dried with a current of air and powdered. We call it "1860." It contains both secretin and cholecystokinin.

The "1852" Method: One gram of the "A pH 1802" powder is dissolved in 30 cc. H_2O. To this is added 70 cc. of absolute ethyl alcohol and 1 cc. of concertrated HCl. The resulting solution is occasionally cloudy. To this solution one volume of acetone is added. A flocculent precipitate results which we call "1851." This is removed by spinning and acetone is added to the filtrate ("1851" filtrate) to make a total of five volumes of acetone. The resulting precipitate, which is called "1852," contains some secretin and most of the cholecystokinin. It is collected by centrifugalizing and dried. Adding acetone to this filtrate up to ten volumes precipitates the remainder of the secretin, which is called "1854."

The method for assaying cholecystokinin previously described was used (Ivy and Oldberg, 1928).

Results: The "1860" method has been checked more than thirty times on six different batches of "A pH 1802" powder. In our hands it has uniformly yielded cholecystokinin in doses of from 2.0 to 3.5 mgm. in dogs weighing approximately thirty pounds, the smallest per kilogram dose being 0.05 mgm. per kgm. body weight. The recovery of cholecystokinin by this method is practically complete. A typical experiment is as follows: One gram of "A pH 1802" powder, which caused gall bladder contraction in 6 mgm. doses, was used. We obtained 0.505 mgm. of "1860" which was active in 3 mgm. doses. This particular product gave a pancreatic response in 1.4 mgm. doses, the original dosage in the "A pH 1802" powder being approximately 2.0 mgm. (See Table I).

Using the "1852" method, ten trials were made on three different batches of "A pH 1802" powder. On assay the milligram dosages necessary to cause a 1 cm. rise in intra-gall-bladder pressure were as follows: (1) 3.3, (2) 3.0, (3) 2.8, (4) 2.5, (5) 3.0, (6) 3.5, (7) 2.8, (8) 2.0, (9) 2.7, (10) 2.5. The "1854" precipitate when injected into dogs of approximately thirty pounds body weight causes the pancreas to secrete in 1.0 mgm. or less doses.

Method of arriving at the dosage: The response of the gall bladder of different dogs varies considerably. This variation, we believe, depends chiefly on the depth of the anesthesia and on the extent that the blood supply of the gall bladder has been disturbed. We keep on hand a number of different preparations of cholecystokinin, the activity of which is known. When a new preparation is to be tested, we first inject the "known" or control solution and in this way determine if the dog has a responsive gall bladder. If so, we then inject the "unknown" solution. We consider a rise of 1 cm. in intra-gall bladder pressure a threshold dose.

TABLE I.

CHOLECYSTOKININ YIELDS USING THE "1860" METHOD.

Ten experiments in which complete record of yields was made.* Hog material used.

Experiment No.	"A pH 1802" Powder	Dosage, mgm.	Weight "1860" Powder, mgm.	Dosage mgm.
1	1.000	6.0	0.505	3.0
2	1.000	6.0	0.470	3.8
3	1.000	7.0	0.465	3.0
4	1.000	7.0	0.468	3.1
5	1.000	6.0	0.470	3.0
6	1.000	8.0	0.275	2.8
7	1.000	8.0	0.272	3.0
8	1.000	6.0	0.456	3.4
9	1.000	6.0	0.405	2.5
10	1.000	6.0	0.426	2.9

*Secretin dosages are not given. A better method for preparing secretin will be given in a following paper.

The variations in dosage are due to two factors, (a) the variation from dog-to-dog and other experimental factors beyond our control, and (b) the variation in purity of the product. We do not believe that our method will yield an absolutely uniform product, and claim only that it will vary within the limits given above.

Both our "1860" and "1852" products must be further purified before extensive human experiments are indicated. This product, however, is non-antigenic in the guinea pig and non-toxic in the dog. So we believed that a few experiments might be undertaken on human beings.

EXPERIMENTS ON MAN

Five normal subjects (medical students) and three dispensary patients volunteered for the experiments.

The gall bladder was visualized with tetraiodophenolphthalein. From 25 to 30 mgm. of our product in aqueous solution (redistilled water and Berkefeld filtration) were injected at ten-minute intervals for one hour in the normal subjects and for one-half hour in the patients. X-ray pictures were made at 10 or 30-minute intervals.

In the first subject (L.A.C.) it was obviously necessary to experiment with the dosage. In this subject we failed to obtain definite evidence of emptying.

In the four normal subjects in which the above stated dosage was used, all manifested some degree of gall bladder evacuation with change in contour as was observed previously in dogs. In one (H.C.L.), the evacuation was complete; in the three others it was partial. Two of the five normal subjects felt "light-headed" from one-half to one hour after completion of the injections, which sensation disappeared within 30 minutes or one hour, no other symptoms being experienced.

The three patients in whom gall bladder disease had been suspected, but whose gall bladders visualized, received three doses at 10-minute inter-

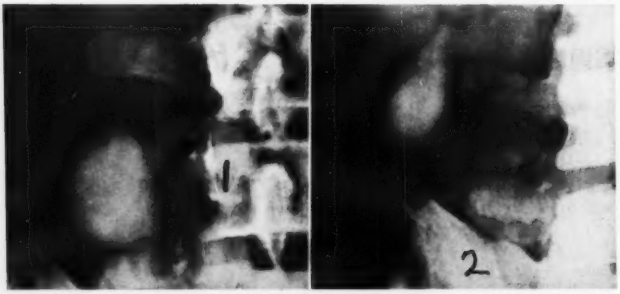

Figure 1. The gall bladder of a patient (man) with a pericholecystitis before (1) and after (2) the injection of three doses of cholecystokinin. Change in gall bladder becomes evident within five or ten minutes after the first injection. The second picture was taken about 45 minutes after the first.

Figure 2. The gall bladder of a patient (woman) with suspected cholecystitis before (1) and after (2) the injection of three doses of cholecystokinin. The second picture was taken about 45 minutes after the first.

vals. Two of the three showed a definite decrease in the size of the gall bladder. One of the two had a peri-cholecystitis, which did not interfere with gall bladder evacuation, but was sufficient to cause symptoms. This patient about 1½ minutes after the second injection began to itch at various points as if he had been bitten by an insect and wheals appeared at the point of scratching. The itching and wheals disappeared within 3 minutes. This phenomenon occurred again after the third injection. The patient

who showed no emptying developed a chill about half an hour after the third injection. This patient complained of being "nervous" and chilly prior to the injection. We believe that the chill she had was probably due to the injection, although our normal subjects failed to manifest a similar reaction. This caused us to stop our work until a more highly purified preparation became available.

In our normal subjects a definite contraction or change in contour of the gall bladder was detectable in the "ten-minute" plate after the first injection, which was observed in dogs by Ivy and Oldberg.

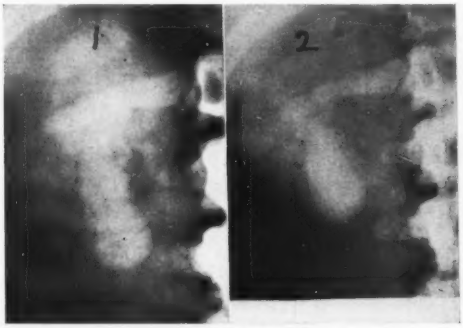

Figure 3. The gall bladder of a student (A.C.) before (1) and after (2) the injection of five doses of cholecystokinin at 10-minute intervals. Only partial evacuation occurred. Picture "one" was taken at 10:00 A. M. and "two" at 11:05 A. M.

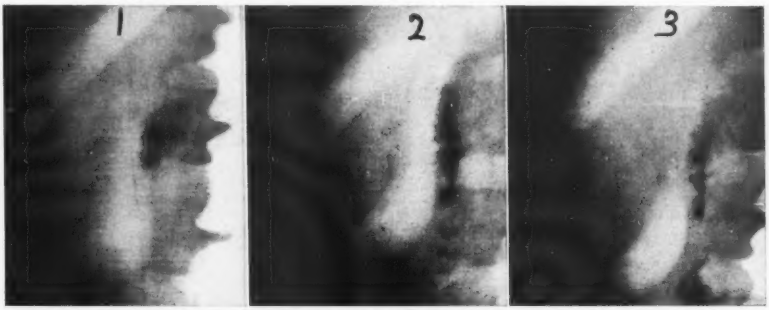

Figure 4. The gall bladder of a student (Hol.) before (1), during (2) and after (3) the injection of six doses of cholecystokinin. Picture "one" was taken at 10:00 A. M., "two" at 10:30 A. M., and "three" at 11:05 A. M.

DISCUSSION

This work raises the question of the therapeutic value of cholecystokinin. Since it is well established that egg yolk and cream by mouth lead to evacuation of the gall bladder within several hours, the authors doubt the therapeutic value of this active principle, in that cholecystokinin must be given intravenously and will do nothing apparently that egg yolk and cream will not do. All that can be claimed for cholecystokinin is that it does act more quickly, as might be expected.

This work does indicate in connection with the observations on dogs that a hormone mechanism for gall bladder contraction and evacuation exists in man.

CONCLUSION

1. The gall bladder of man can be caused to contract and evacuate on the intravenous injection of a "purified" extract of the upper intestinal mucosa, the active principle of which has been called cholecystokinin.

2. A method is described for preparing a cholecystokinin concentrate active in the dog in 3.0 to 1 mgm. doses, or 0.2 to 0.1 mgm. per kilo body weight, and non-antigenic in the guinea pig and non-toxic in the dog, but which produces an occasional reaction in man.

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THE PLUMAGE AND OVIDUCT RESPONSE TO THE FEMALE HORMONE IN FOWLS*

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We have reported in detail (Juhn and Gustavson, 1) the first observations on the assumption of female plumage by male fowls and the functional development of the oviduct of immature pullets subsequent to injections of female hormone prepared from human placentae.

Since, we have repeated these findings, with entirely comparable results with female hormone prepared from human pregnancy urine, using both the immature oviduct and the plumage as tests, and with female hormone prepared from cow placenta and with untreated human pregnancy urine, using the feathering alone as test.

These experiments, recorded here, thus further corroborate the original observations and extend the source for female hormone, effective in modifying the secondary sex characters of birds.

The biological observations were carried out as part of the program on the biology of sex now continued under the direction of Professor F. R. Lillie at the Whitman Laboratory of Experimental Zoology, the University of Chicago. The female hormone was prepared in the Department of Chemistry, the University of Denver and the Department of Physiological Chemistry, the University of Chicago.

The following procedure was used to prepare the hormone from cow placentae. The frozen material was ground in a meat grinder and treated with 1500 cc. of 95 per cent ethyl alcohol for every kilogram of placentae. After 48 hours the alcohol was filtered through a cloth and pressed out. The alcoholic filtrate was evaporated to a small volume and extracted three times with benzene. The benzene was removed by evaporation and the residue taken up with 70 per cent alcohol and extracted three times with one-fourth its volume of hexane. It is important that the 70 per cent alcohol should not contain more than 5 per cent solids. The 70 per cent alcoholic filtrate was then evaporated to dryness and the residue extracted with ether and 5 volumes of acetone added. The mixture was cooled to —10° C. and allowed to stand at that temperature over night. The supernatant liquid was removed by filtration and the filtrate evaporated to dryness and taken up in olive oil.

The preparation from urine was made by the following method: Urine from pregnant women was made acid to Congo Red with acetic acid and extracted in a continuous extractor with ether. The ether was removed by

*The expenses of this investigation were supported in part by the Committee for Research in Problems of Sex of the National Research Council; grant administered by F. R. Lillie.

evaporation and the residue dissolved in 5 per cent sodium hydroxide and again extracted with ether. This material was dissolved in olive oil.

All the female hormone preparations used were assayed in advance in rat units.

The birds belonged to the Whitman Laboratory stock of Light Brown Leghorns. This breed shows a pronounced plumage dimorphism, the feathering of the male and the gonadless bird is identical and differs from that of the female.

The response of the immature oviduct was studied in immature pullets. The hormone was injected over a given time and the test birds and their controls then autopsied and the weight and histological appearance of the treated and normal oviducts ascertained.

For the plumage changes, capons only were used in this series. The procedure was identical with the one employed previously and consisted in plucking feathers in definite regions and injecting the female hormone subcutaneously during the time of feather replacement, a period of about three to four weeks.

The records for each individual in both classes of birds included comb size and body weight during the experimental period, and in the case of the pullets a final autopsy with special reference to the condition of the ovary.

1. Experiments with female hormone prepared from human pregnancy urine. *Extract No. 1289, 40 rat units per cc.*

a. Effects on the oviduct. Pullet No. 358, age 115 days, was injected daily, subcutaneously, with 36 rat units, or approximately four rat units per 100 grams body weight for ten days. The total injected was 360 rat units.

Initial records, August 8, 1929, showed: Comb length, 3.1 cm.; comb depth, 1.3 cm.; body weight, 910 grams. Final records, August 17, 1929, showed: Comb length, 3.4 cm.; comb depth, 1.7 cm.; body weight 981 grams. On August 18, 1929, the pullet was autopsied. There was no inflammation at the sites of injection. The skin, muscle tissue and internal organs were all normal. The ovary was immature and the oviduct coiled and vascular. The weight was 1.5792 grams. Histological investigation showed the development in the treated duct of tubular glands and the muscle coat.

On the same date two control pullets of the same age and lot were autopsied. Pullet No. 317 showed: Comb length, 3.9 cm.; comb depth, 1.9 cm., and body weight, 967 grams. Pullet No. 343 showed: Comb length, 3.6 cm.; comb depth, 1.7 cm., and body weight 864 grams. The ovaries in both birds were in the immature stage. The oviducts of the two control pullets weighed 0.2959 grams and 0.3912 grams, respectively. Neither of the control oviducts showed the development of tubular glands or muscle layer.

b. Effects on the plumage. Capon 28-537 received subcutaneous injections of 88 rat units or 4 rat units per 100 grams body weight, daily, with the exception of Sundays, for about three weeks. Feathers were plucked the day before beginning injections, at intervals during, and two days after injections were interrupted. The records for the experimental period are compiled below:

Capon 28-537:

Date	Weight, gms.	Comb, cm.		
		L.	D.	
8/ 8/29	2210	5.3	2.1	Feathers plucked, breast, saddle.
8/ 9/29	....	...	...	Injections begun.
8/15/29	2225	5.3	2.3	Feathers plucked, breast, saddle.
8/22/29	2288	5.5	2.3	Feathers plucked, breast, saddle.
8/27/29	....	...	...	Injections discontinued.
8/29/29	2334	5.5	2.5	Feathers plucked, breast, saddle.

The replacing plumage in the regions plucked the day before beginning injections was entirely female in breast and saddle. The one-day interruption of injections was recorded, exactly as noted in the earlier observations, by a black, male bar in the salmon, female, breast feathers. The saddle feathers remained unaffected by this diminution of hormone concentration as also noted previously. See Figures 4 and 8.

This differential sensitivity of the feathers in the breast and saddle to a diminution of female hormone concentration is correlated with the difference in growth rate present in the regenerating plumage in the two regions.

The incoming plumage in the regions plucked after the injections were interrupted was entirely male. See Figures 1 and 5.

The replacing plumage in the regions plucked after the injections were under way showed female tips and male bases. The proportion of female to male varied according to the length of time the regenerating feathers were under the influence of the female hormone and thus furnished a preliminary means of estimating the persistence of the hormone in the organism in concentrations effective in causing female plumage modifications. See Figures 2, 3, 6 and 7. This special question has since been further studied and a preliminary report of the experimental results published (Juhn, Faulkner and Gustavson, 2).

2. Experiments with female hormone prepared from cow placentae. *Extract No. 1315, 50 rat units per cc.*

Effects on the plumage. Capon 29-986 received 110 rat units daily, or approximately 8 rat units per 100 grams body weight, subcutaneously, for 23 days.

It was found earlier that a positive response to the female hormone could be determined only after the time required—at least two weeks—for the plucked feathers to regenerate and pierce the sheath. More rapid readings seemed possible by allowing plumage regeneration to proceed for

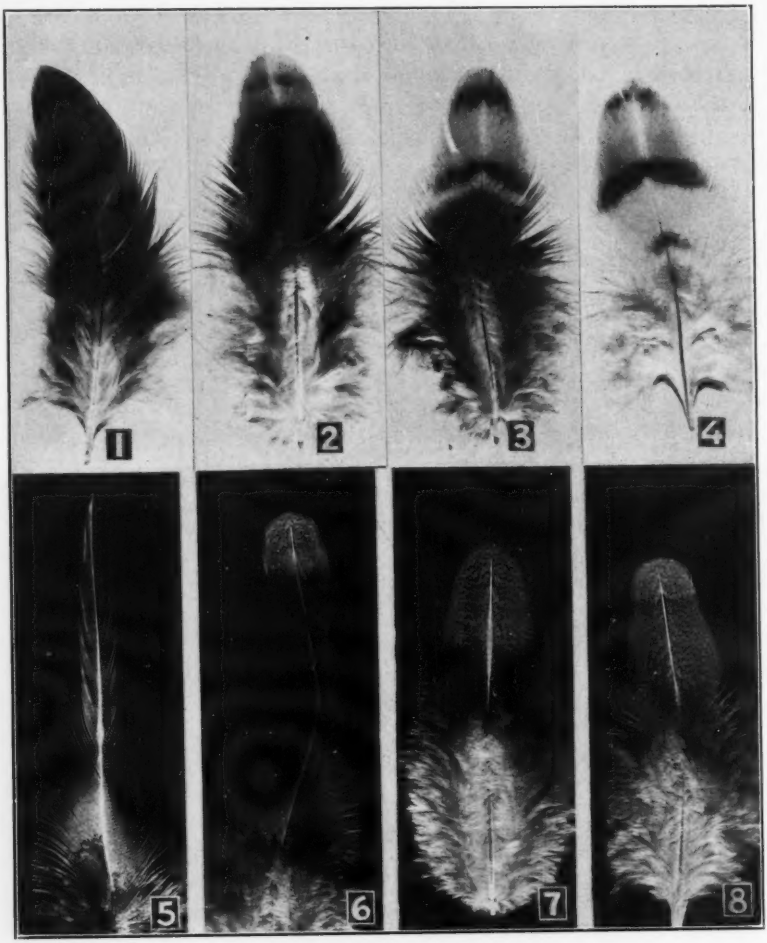

PLATE I

EXPLANATION OF FIGURES

Exp. I. Capon 28-537. Female plumage modifications subsequent to injections of female hormone prepared from human pregnancy urine.

1. Male breast feather from region plucked after injections were discontinued.

2. Breast feather from region plucked towards end of period of injection showing narrow female tip and male base.

3. Breast feather from region plucked during first half of period of injections showing wide female tip and male base.

4. Entirely female breast feather from region plucked at the time of beginning injections. Note narrow black male bar recording one-day weekly interruption of injections.

5. Male saddle feather from region plucked after injections were discontinued.

6. Saddle feather froom region plucked towards end of period of injection showing narrow female tip and long male base.

7. Saddle feather from region plucked during the first half of period of injections showing wide female tip and male base.

8. Entirely female saddle feather from region plucked at the time of beginning injections.

some time before beginning injections. Accordingly, feathers were plucked 14, 10 and 6 days before injections of the female hormone were started. The records are compiled below.

Capon 29-986:

Date	Weight, gms.	Comb, cm.		
		L.	D.	
10/10/29	1488	5.0	2.6	Feathers plucked, breast, saddle.
10/16/29	1531	5.0	2.6	Feathers plucked, breast, saddle.
10/21/29	1588	5.0	2.6	Feathers plucked, breast, saddle.
10/24/29	1588	5.1	2.4	Injections begun.
10/30/29	1624	5.1	2.6	
11/ 5/29	1672	5.1	2.5	
11/13/29	1733	5.0	2.6	
11/16/29	....	...	...	Injections discontinued.
11/18/29	1762	5.1	2.6	Feathers plucked, breast, saddle.

The feathers in the regions plucked 14 and 10 days before beginning injections showed male tips and female bases; the feathers plucked 6 days before were entirely female. The incoming plumage in the regions plucked after injections were discontinued was entirely male.

The response to the female hormone was most rapidly ascertained, in about six days, in the breast feathers of the region plucked 14 days before the injections were begun. This observation was the basis for the development of a method permitting of more rapid readings yet, within 72 hours and with smaller quantities of the hormone (Juhn and Gustavson, 3).

3. Experiments with human pregnancy urine.

The material was filtered through a Berkefeld candle and kept in the ice-box. Just previous to injection the amount required was warmed to body temperature.

The effects on the plumage were studied in two adult capons, No. 29-939 and No. 29-984. Feathers were plucked in the breast only ten days before beginning injections. Each bird then received 40 cc. of the urine injected subcutaneously daily for 7 days. The amount was distributed in two doses of 20 cc. each administered in the morning and late afternoon, respectively.

The regenerating plumage showed distinct female modifications in the shape of a wide female bar in the male breast feather. There were no changes in the head-furnishings and while the injections caused some local irritation, the general condition of both capons continued good during the entire experimental period.

In conclusion it may be said that the female hormone prepared from human pregnancy urine, the untreated pregnancy urine as such and the female hormone prepared from cow placentae are equally effective in causing female plumage modifications in male fowls when administered in adequate dosages.

SUMMARY

The effects of injections of female hormone prepared from cow placentae and human pregnancy urine on immature brown leghorn pullets and adult brown leghorn capons has been studied.

Hypertrophy of the oviduct takes place in the pullet, involving development of tubular glands and the muscle coat.

In adult capons feathers regenerating from plucked areas are of the female type during the period of injecting female hormone.

Failure to inject the birds one day a week is recorded by a bar of black (male) pigment in the breast feather, but the interruption of injections is not recorded in the saddle feathers.

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STUDIES ON FAT METABOLISM
II. THE EFFECT OF CERTAIN HORMONES ON FAT TRANSPORT*

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In the preceding paper (1) of this series a preliminary investigation of the lipemia resulting from the ingestion of a fat test-meal in normal and obese subjects was made. A study of the "fat tolerance" and "sugar tolerance" of the obese subjects indicated that a correlation existed, which suggested along with other evidence the view that either insulin or the mechanism controlling carbohydrate mobilization promotes the deposition of tissue fat when fat is absorbed.

This study was undertaken to determine in dogs the effect of starvation, sugar feeding, insulin, pituitrin, and epinephrin on the blood fat curve following the ingestion of a test-meal of fat.

Methods: Adult dogs weighing from thirty to forty pounds were used. The fat meal consisted of 2 cc. of olive oil per pound weight given by stomach tube. Venous blood was removed (8-10 cc.) before and at certain intervals after the meal and the plasma analyzed for total fatty acids and cholesterol by Bloor's new method (2).

Starvation: The relation of starvation to alimentary lipemia was studied because in starvation the carbohydrate reserve of the body is markedly reduced and fat is mobilized from the fat depots, which might be expected to modify the alimentary lipemia.

Considerable work has been done on the effect of starvation on the fat of various tissues, especially the liver, heart and muscle with variable results. The effect of starvation on blood fat is within the limits of normal variation (3). Bang (4), as a result of his work, stated that because of the effect of nutrition on alimentary lipemia, it is necessary to use starved dogs, a generalization which is indicated by our results.

In the first part of our work we gave the fat meal 15 hours after the preceding meal, no attention having been paid to the character of the last meal, the stock diet being bread, yellow corn meal, and bone soup. Most of the dogs responded with a definite increase in blood fat after the test-meal beginning about two hours after and lasting from 10 to 12 hours. Some, however, showed little or no increase in blood fat which has been observed by other workers in this field. It was found that the marked variation can be eliminated by starving the animals several days (7-14 days) before the test. This was demonstrated by fat tolerance tests performed in the same

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animal in the fasting and well-fed condition. Water was allowed ad libitum. During the feeding period the dog was given all that he would eat twice daily.

Table I shows the results in four dogs which failed to show alimentary lipemia on 24-hour starvation or less.

TABLE I

SHOWING EFFECT OF STARVATION ON ALIMENTARY LIPEMIA IN DOGS THAT FAILED TO MANIFEST LIPEMIA UNLESS STARVED

Dog	Lbs. Weight	Feeding Period	Starvation	Total Fatty Acids, mgm. %				
				Before	2 Hours	5 Hours	7 Hours	
10	35	7 days	16 hrs.	312	325	336	327	70 cc. olive oil each test.
			12 days	228	554	580	510	
		10 days	24 hrs.	285	295	321		
12	34		13 days	382	494	610		
		10 days	24 hrs.	285	270	316		
21	36		7 days	305	488	560		
		7 days	17 hrs.	266	275	280		
13	33	4 days	16 hrs.	352	347	340		
			3 days	350	390	415		
			7 days	266	350	424		

The results show that after abundant feeding the "fat tolerance" is "high," and after fasting 3-13 days it is "low." The state of nutrition of the dog modifies the alimentary blood fat curve but does not materially affect the continuous blood fat level.

In most of the work described from now on in our paper the dogs were starved from one to two weeks before the test-meal of fat was administered.

Sugar Administration: Since the nutritional condition has an effect on the alimentary blood fat curve, it was considered significant to determine the effect of glucose administration on the blood fat curve.

Bang (4) found that the administration of bread (5 experiments) exercised a strong inhibitory effect on the alimentary lipemia in dogs and concluded that a liver rich in glycogen prevents fat from accumulating in the blood. McClure and Huntzinger (5) found that the ingestion of all types of food-stuffs in man causes an increase in blood fatty acids, carbohydrates causing the smallest.

TABLE II

SHOWING THAT THE ORAL ADMINISTRATION OF GLUCOSE WITH THE FAT MEAL PREVENTS ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Total Fatty Acids, mgm. %		
		Before	After 2 Hours	After 5 Hours
114	8	259	275	285
115	10	219	210	221
116	10	345	354	350
118	7	316	318	325
119	13	326	340	322
*117	9	259	461	316

*In this dog the glucose was given two hours after the olive oil.

In five experiments one gram of glucose per pound of body weight in 20 per cent solution was given by stomach tube along with the olive oil to dogs known to respond with an alimentary lipemia on fat administration. The results are shown in Table II.

It is quite evident from these experiments that the oral administration of glucose prevents or markedly reduces the alimentary lipemia.

Since the glucose was given by mouth the question arises as to whether or not the absorption of the fat was modified. For this reason it was deemed advisable to administer the glucose parenterally.

In three experiments glucose was administered intravenously. The results are shown in Table III.

TABLE III

SHOWING THAT THE INTRAVENOUS ADMINISTRATION OF GLUCOSE PREVENTS ALIMENTARY LIPEMIA

Dog No.	Starvation Days	Procedure	Cholesterol %	Total Fatty Acid, %
58	4	12:00—70 cc. olive oil by stomach tube.	0.138	0.360
		3:30—50 cc. 20% glucose intravenously.	0.111	0.682
		4:30	0.105	0.388
59	8	11:15—80 cc. olive oil by tube and 50 cc. of 20% glucose intravenously.	0.095	0.443
		1:30	0.110	0.449
		3:30	0.126	0.618
54	6	11:35—80 cc. olive oil by tube.	0.097	0.510
		1:50—50 cc. of 20% glucose intravenously.	0.095	0.643
		3:30	0.097	0.526
		4:25	0.092	0.525

In three other experiments glucose was given hypodermically (Table IV).

It appears from these experiments that the parenteral administration of glucose also prevents or reduces the alimentary lipemia.

Insulin: Macleod (6) found that insulin decreases the blood and liver fat in diabetic dogs. That insulin has a remarkable effect on diabetic lipemia has been repeatedly observed in the clinic [Joslin (7), Rabinowitch (8), Chauffard and Labbe (9), Fonseca (10)].

TABLE IV

SHOWING THAT THE SUBCUTANEOUS ADMINISTRATION OF GLUCOSE PREVENTS ALIMENTARY LIPEMIA

Dog No.	Starvation Days	Procedure	Cholesterol %	Fatty Acid Total, %
60	5	10:00—80 cc. oilve oil by tube and 200 cc. 10% glucose subcutaneously.	0.158	0.504
		1:45	0.151	0.534
		2:45	0.160	0.553
60	8	12:00—100 cc. oilve oil by tube.	0.125	0.335
		2:30—300 cc. 10% glucose subcutaneously.	0.172	0.554
		4:00	0.172	0.460
61	10	10:30—80 cc. olive oil by stomach tube and 150 cc. 10% glucose subcutaneously.	0.138	0.440
		11:30—200 cc. 10% glucose subcutaneously.	0.161	0.445
		1:30	0.130	0.462
		3:00	0.136	0.485

Just how insulin brings about this change is not known. According to Chauffard and Labbe (9) insulin influences fat metabolism independently of its effect on carbohydrate metabolism. Wertheimer (11) finds that insulin prevents lipemia and fatty infiltration of the liver in phlorizin poisoning and causes the phlorizin lipemia to disappear and the fatty liver to return to normal. Dudley and Marrian (12), however, find that the amount of fatty acids in the liver was not changed in normal starved mice following insulin, which was confirmed by Raper and Smith (13). Wertheimer (11), Labbe and Tamalet (14) and Schmidt and Saatchian (15) report that insulin hypoglycemia is associated with decreased blood cholesterol, the latter observers finding that the fatty acids were affected more than cholesterol. White (16) reports a slight rise in blood fat after insulin. In this connection it is interesting to note that Shih-Hao and Mills (17) found that insulin decreases blood cholesterol and fat in nephrosis without materially affecting the blood sugar level, which indicates that insulin causes deposition or disappearance of blood fat irrespective of blood sugar level. Raper and Smith (13) conclude that fat synthesis in the liver is not associated with insulin hypoglycemia and believe that in the light of our present knowledge it is impossible to correlate changes occurring in blood fat with those occurring in the liver. But Bang (4) takes the position that the diabetic organism is more or less unable to deposit absorbed fat in the tissues, the liver being chiefly at fault.

Onohara (18), as far as we have been able to find, is the only one who has directly studied the effect of insulin on alimentary lipemia in normal dogs. He studied two dogs and found the lipemia to be reduced in one but not the other. He paid no attention to the nutritional state of the animals. Hartmann (19) found that in man the ingestion of 50 gm. of butter and 20 gm. of oatmeal caused a slight rise in blood fat at 1 hour which returned to normal in 4 hours. In his cases insulin caused a slight decrease in blood fat and did not modify to a significant degree the blood fat curve after the ingestion of his test-meal. It is to be noted that he used carbohydrate with fat in his test-meal.

We desired first to study the effect of insulin on the fasting blood fat level. In three dogs starved for seven or eight days, insulin sufficient to

TABLE V

SHOWING THAT INSULIN PREVENTS ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Amount of Insulin Units	Total Fatty Acid, mgm. %		
			Before	2 Hours	5 Hours
102	8	20	305	314	310
103	10	30	289	268	304
105	7	25	410	425	432
106	14	25	324	316	318
107	10	30	194	176	205
108	12	40	343	340	338
109	8	30	259	....	270
110	11	25	415	428	402

lower the blood sugar to 0.038 - 0.024 gm. produced no changes in the fasting blood fat.

In eight other dogs we studied the effect of insulin on alimentary lipemia. In these experiments the dogs were fasted for from seven to fourteen days and the insulin was given hypodermically at the same time the fat meal was given. The results are shown in Table IV and demonstrate that insulin prevents alimentary lipemia in normal dogs that have been fasted.

Epinephrin: Alpern and Collazo (20) report that epinephrin depresses slightly the blood cholesterol and blood fat values. Fleisch (21) finds that intravenous epinephrin (0.1-1 mgm.) causes a slight decrease in blood fat and cholesterol, whereas given subcutaneously in larger doses (3 - 6 mgm.), it causes a marked increase of blood fat and cholesterol at the end of 24 hours. Jollson and Shoor (22) find that adrenalin has no effect on blood cholesterin in adrenalectomized dogs.

In the experiments shown in Table VI the effect of adrenalin was studied on the fasting blood fat level. No definite changes occurred in the blood fat or cholesterol.

TABLE VI

SHOWING NO EFFECT OF EPINEPHRIN HYPODERMICALLY ON BLOOD FAT OF NORMAL FASTING DOG

Dog No.	Procedure	Time	Total Fatty Acid, %	Blood Sugar, %	Cholesterol %
2	Fasting 2 days. 3 mgm. adrenalin at 10:00.	10:00	0.554	0.089	0.258
		11:00	0.512	0.160	0.230
		12:00	0.548	0.142	0.210
		1:00	0.582	0.118	0.235
4	Fasting 2 days. 2.5 mgm. adrenalin at 10:00.	10:00	0.367	0.101	0.128
		11:00	0.349	0.230	0.117
		12:00	0.385	0.240	0.115
		1:00	0.338	0.247	0.107
		2:00	0.390	0.250	0.107
9	Fasting 5 days. 2.0 mgm. adrenalin at 12:00.	12:00	0.216		0.106
		2:00	0.234		0.073
		4:15	0.220		0.095
56	Fasting 24 hours. 4.5 mgm. adrenalin March 19th, 11:45.	11:45	0.726	0.087	0.133
		2:30	0.772	0.231	0.141
	(March 20)	10:00	0.692	0.092	0.173
		3:00	0.715		0.152
	(March 21)	3:00	0.526		0.241
58	Fasting 7 days. 5 mgm. adrenalin April 14, 11:00 A.M.	11:00	0.520		0.145
	(April 15)	11:00	0.507		0.147
	(April 16)	11:00	0.532		0.166

In further experiments the dogs were fasted and then given from 2 to 3 mgm. of epinephrin subcutaneously along with the fat meal. The results are shown in Table VII. The data obtained do not differ materially from the normal fat tolerance values obtained in fasting dogs not receiving epinephrin.

So epinephrin as administered had no effect on the alimentary lipemia of these dogs, nor on the fasting blood fat level.

TABLE VII

SHOWING EFFECT OF EPINEPHRIN SUBCUTANEOUSLY ON ALIMENTARY LIPEMIA OLIVE OIL, 70 CC. AND ADRENALIN, 2-3 MGM. WERE ADMINISTERED

Dog No.	Fasting Days	Total Fatty Acids, mgm. %			
		Before	2 Hours	5 Hours	7 Hours
*114	8	401	510	770	609
*115	7	429	507	623	582
*116	12	354	446	563	429

*Note response to glucose and fat in Table II.

Insulin and Epinephrin: The question arose whether epinephrin might not antagonize the action of insulin on blood fat, since it antagonizes the effect of insulin on blood sugar. This might not be predicted, however, since it was pointed out above in the discussion of the literature on the effect of insulin on blood fat that insulin caused deposition of fat irrespective of blood sugar level. The results are shown in Table VIII. The epinephrin did not antagonize the insulin action, although there was not sufficient epinephrin absorption to prevent the blood sugar from falling.

TABLE VIII

SHOWING THAT AS THE EXPERIMENTS WERE PERFORMED EPINEPHRIN FAILED TO ANTAGONIZE THE EFFECT OF INSULIN ON ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Total Fatty Acids, mgm. %				Blood Sugar, Mgm. %	
		Before	3 Hours	4 Hours	5 or 7 Hours		
117	7	354	460	409	377	84–50	Insulin and epinephrin given at 3rd hour.
118	7	382	405		401		Insulin and epinephrin given with fat.
120	11	404	415		436		Given with fat.

Dosage insulin 25 units and epinephrin 3 mgm. intramuscularly.

Pituitrin: Coope and Chamberlain (23) found that the injection of pituitrin into rabbits caused a definite increase in the fat of the liver. Studies of blood fat were not made.

Our experiments were performed by injecting two ampules of (obstetrical) pituitrin intramuscularly at the same time the fat meal was given. The results are shown in Table IX.

TABLE IX

SHOWING THAT PITUITRIN HAS NO EFFECT ON ALIMENTARY LIPEMIA

Dog No.	Fasting Days	Total Fatty Acids, %		
		Before	3 Hours	5 Hours
72	7	0.520	0.636	0.713
73	8	0.381	0.520	0.595
118	8	0.410	0.533	0.605

The results show that the pituitrin had no appreciable effect on lipemia following the fat meal.

DISCUSSION

After ingestion of fat there is a continuous absorption of the fat from the intestine into the blood stream, and simultaneously a continuous passage of the fat from the blood stream into the tissues. The alimentary lipemia curve represents the difference in the rate of these two processes. The alimentary lipemia curve may be compared with the alimentary glycemia curve which represents the difference between the rate of sugar absorption and sugar "utilization." "Sugar tolerance curves" are usually interpreted as expressing the rate of sugar "utilization." The rate of the passage of the fat into the blood stream after ingestion of fat, is, of course, a more complicated process, since it includes also the rate of the digestion of the fat, which depends on bile and pancreatic juice secretion, etc. Yet it is probably safe to say that under standard experimental conditions in the presence of normal digestive organs, the rate of the fat digestion and absorption is fairly uniform. With this precaution, alimentary lipemia curves may be considered as approximate measures of the rate of fat "utilization."

On this basis, our experiments indicate that insulin markedly promotes the passage of ingested fat from the blood stream into the tissues. If sufficient doses of insulin are given, all ingested fat passes from the blood stream without appreciably elevating the blood fat level at any moment. This is the more remarkable since insulin has no definite effect on the fasting blood fat level.

Does insulin promote the passage of the ingested fat from the blood stream by direct action, or is this effect of insulin secondary to its effect on carbohydrate metabolism? That the effect of insulin on the blood fat is not a consequence of the insulin hypoglycemia is evident from the fact that administration of sugar had the same effect in our experiments. These observations along with the failure of epinephrin hyperglycemia to prevent alimentary lipemia suggest strongly that the effect of insulin on alimentary lipemia is independent from its effect on the *blood sugar*. But at the same time it shows that the deposition of ingested fat is in some way dependent on carbohydrate metabolism. Apparently the type of carbohydrate metabolism going on in the *tissues* or in some specialized tissue such as the liver is the factor controlling the passage of ingested fat from the blood stream into the tissues; or it might be said that glycogen formation favors fat deposition.

It is worthwhile to recall at this juncture Wertheimer's findings on the effect of insulin on another phase of fat transport, namely, on fat mobilization in phlorizin poisoning. Wertheimer found that insulin inhibits the passage of fat from the fat depots into the blood and into the liver in phlorizin poisoning. He did not determine whether sugar admin-

istration has a similar effect. But it has been known for a long time, and was observed by Wertheimer also that in order to obtain marked fat accumulation in the liver and ketosis through phlorizin poisoning, the animals have to be starved for several days (24). Our experiments show that starvation also promotes the accumulation of the ingested fat in the blood. It seems, then, that starvation has the same effect on fat transport whether the transported fat is ingested fat or mobilized depot fat. Now, one of the chief changes in the body after brief starvation is a decrease in the carbohydrate reserve of the body which again suggests a dependence of fat transport on the carbohydrate metabolism of the tissues. This relation may be expressed in the following way: the promotion of carbohydrate synthesis and oxidation favors the fixation of fat in the peripheral tissues; a decrease of carbohydrate synthesis and oxidation promotes the accumulation of fat in the blood and liver.

SUMMARY AND CONCLUSION

1. It was shown experimentally in dogs that fasting augments and previous abundant feeding decreases alimentary lipemia.

2. The administration of glucose either by mouth or parenterally inhibited alimentary lipemia in fasting dogs.

3. Insulin and epinephrin had no definite effect on the fasting blood fat of dogs.

4. Insulin was found to inhibit alimentary lipemia.

5. Epinephrin and pituitrin had no definite influence on alimentary lipemia.

It was concluded that carbohydrate metabolism plays an important, if not essential role in the regulation of the blood fat level of normal dogs during the alimentary absorption of fat.

We desire to express our thanks to Dr. A. C. Ivy for his interest and advice.

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Book Reviews

THE NEW CRIMINOLOGY. Max Schlapp and Edward H. Smith. 1928. Boni and Liveright, N. Y. Pp. 325.

This volume is a combination of interesting sociology, fair psychology, poor psychiatry and incredibly bad endocrinology. In a sentence, the burden of the book is that criminality is due to hormone imbalance in the mother during gestation of the future criminal.

L'HYPOPHYSE. H. Penau, L. Blanchard and H. Simonnet. Les Presses Universitaires de France, Paris, 1929.

L'hypophyse is a complete summary, in French, of the most important investigations upon the hypophysis carried out, prior to 1928, in France, Germany, England and the United States. The literature reviewed in the book is listed in a carefully prepared bibliography containing titles of 575 papers and monographs. The authors are to be commended for the excellent way in which they have evaluated the experimental work reported by the various writers. The authors of L'hypophyse have prepared many tables and charts to aid the reader in understanding and grasping the significance of steps in the preparation of extracts and the results of tests on animals. Anatomy, histology, chemistry and pharmacology of the anterior and posterior lobes are covered in a thorough manner up to 1928. So much progress has been made in the last two years in the study of the anterior lobe that the book is already out of date in that phase.

Clinical applications of extracts of the hypophysis are not dealt with as the book is not intended for a physicians' manual. It is an excellent contribution to the scientific literature.

DIE PRAKTISCHE THERAPIE MIT HORMONEN UND VITAMINEN MIT BESONDERER BERUCKSICHTIGUNG AKTUELLER ERNAHRUNGSFRAGEN. Various authors. 1930. Otto Gmelin, München. Pp. 138.

Cited in Endokrinologie, **6**: 234. 1930.

Abstract Department

A tumor of the adrenal gland with fatal hypoglycemia. Anderson, H. B., Am. J. M. Sc. **180:** 71. 1930.

A unique case is reported of a patient in which the only outstanding pathologic finding was a tumor of the left adrenal gland. There was also congestion of the pancreas and pituitary gland. The symptoms were for a time relieved by glucose administration but later glucose failed to relieve the symptoms. Epinephrin was given one or two days before the patient died but without effect. When the blood sugar fell below 0.07 the patient became restless, confused mentally and sweated profusely. The lowest blood sugar noted was 0.04 per cent.—R. G. H.

The selective vasoconstrictor action of adrenaline. Clark, G. A., J. Physiol. **69:** 171. 1930.

When enough adrenaline is administered to cause a rise in blood pressure there is a persistent cutaneous vaso-constriction accompanied by an increased blood volume in skeletal muscle and in the portal area. The latter effect is partly independent of visceral reflexes since it occurs after vagus and splanchnic section. When a rise in pressure is prevented by a mercury compensator there is intestinal vaso-constriction less pronounced than in the skin. This indicates that reduced capacity of the nervous system, increased cardiac activity together with cutaneous vaso-constriction all play a part in the increased blood pressure after adrenaline.—C. I. R.

The mechanism of epinephrine action. VI. Changes in blood sugar, lactic acid and blood pressure during continuous intravenous injection of epinephrine. Cori, C. F., G. T. Cori and K. W. Buchwald, Am. J. Physiol. **93:** 273. 1930.

Observations have been made as to the changes produced in blood sugar and lactic acid of normal rabbits during continuous intravenous injection of epinephrine at rates ranging from 0.00005 to 0.001 mgm. per kilo per minute. The minimal effective rate of injection of 0.00005 to 0.0001 mgm. per kilo per minute produces an increase not only in blood sugar but also in blood lactic acid. This rate of injection is 30 times smaller than the maximal rate of discharge of epinephrine from the adrenals as recorded by Cannon and Rapport and 8 times smaller than the rate of intravenous injection which causes a rise in blood pressure of unanesthetized rabbits. In view of these facts the increase in blood lactic acid after epinephrine injections is regarded as physiologically significant. As soon as the injection is discontinued, both blood sugar and lactic acid begin to fall, showing that epinephrine is destroyed rapidly and that the after effect is of short duration. These points are also illustrated in experiments in which 0.03 mgm. of epinephrine per kilo was injected at once into the blood stream. After such an injection the peak value of blood sugar and lactic acid is reached in 15 minutes or sooner and there is a return to normal in 1 hour. This is in contrast to the sustained and much larger increase in blood sugar and lactic acid to be observed when the same amount of epinephrine is injected in the course of 1 hour. The similarity between the sugar and lactic acid curves in blood observed after subcutaneous and after continuous intravenous injection of epinephrine is emphasized. The smallest rate of injection of epinephrine which causes a perceptible rise in the blood pressure of unnarcotized rabbits is close to 0.00008 mgm. per kilo per minute.—Authors' Summary.

Variability of the abdominal paraganglia in childhood (Variabilitäten der abdominalen Paraganglien im Kindesalter). Iwanow, G., Ztschr. f. Anat. u. Entwcklngsg. **91:** 404. 1929.

Largely topographical. Periods of increase and decrease are plotted to 13 years of age. A rapid increase in number and size occurs during the first year and a half, followed by a slow decline, reaching a minimum at about 5 years of age. The blood and lymph supply is briefly discussed.—A. T. R.

The effects of x-rays on the adrenal gland. Rogers, F. T. and C. L. Martin, Am. J. Physiol. **93**: 219. 1930.

The direct application of x-rays of an intensity estimated as three and one-half human erythema doses to the one exposed adrenal gland of dogs, after the excision of the other gland, produced no subsequent changes in the gland except a slight fibrosis. No functional disturbances appeared in these animals during a period of observation of from three to twelve months after the irradiation. The application of six to eight doses to the adrenal gland produced no observable functional disorders in dogs kept three months after irradiation, although fibrous proliferation in the gland can be demonstrated microscopically. Adrenal deficiency symptoms can be induced in dogs by the surgical excision of one gland and giving excessive x-ray doses to the remaining gland, but the lapse of several months may be required for their appearance. These effects are as follows: the gradual onset of a progressive muscular weakness, depression of metabolism, and terminal lowering of the blood chlorides and death. Heavy dosage of x-rays to the exposed adrenal gland induces degenerative changes, first in the medulla of the gland, and then of the zona reticularis and zona glomerulosa and an extensive proliferation of fibrous tissue throughout the gland.—Authors' Summary.

The effect of restricted diet and suprarenalectomy on experimental tuberculosis in the white rat. Steinbach, M. M., Proc. Soc. Exper. Biol. & Med. **27**: 142. 1929.

Bilateral suprarenalectomy in the rat appears to lower the resistance so that subsequent inoculation with bovine tubercle bacillus results in definite tissue reaction, with tubercle formation and caseation, resembling human tuberculosis. This does not occur in normal rats or in rats on restricted diet. Suprarenalectomy and, to a less extent, deficient diet increase the susceptibility of rats to the avian tubercle bacillus.—M. O. L.

Sulphate retention in dogs following bilateral adrenal extirpation. Swingle, W. W. and W. F. Wenner. Physiol. Zoöl. **1**: 37. 1928. Abst., Biol. Absts. **3**: 1206. 1929.

Acid-base equilibrium tests in adrenalectomized cats show that animals presenting symptoms of adrenal insufficiency are suffering from an uncompensated non-volatile acidosis. The acidosis was attributed to phosphoric and undetermined organic acids (the organic acid including the sulphate ion because of inability to test for it separately). The present experiments show that the sulphate ion plays an important role in the acid intoxication. The chief results are as follows: Retention of inorganic sulphate occurs following the onset of serious symptoms of adrenal insufficiency. Values as high as 14 mgm. are not uncommon. Unilaterally operated dogs and bilaterally operated animals showing no symptoms have normal amounts of inorganic sulphate in the blood, i. e., values ranging from 0.9 mgm. to 2.5 mgm. per 100 cc. The increase in inorganic sulphate parallels the increase in inorganic P and N. Sulphate and phosphate retention are sufficient to account for the degree of acidosis observed in adrenalectomized dogs. Organic acid is not so important a factor in inducing the fall in bicarbonate as the phosphate and sulphate. With the exception of those types of nephritis characterized by N retention and acidosis, adrenal insufficiency is the only other condition where sulphate retention occurs. This is further evidence that the suprarenal cortex is necessary for the maintenance of normal kidney function.

Problems of age (Problemy Stari). Eiselt, R., Bratisl. lekár. listy, **9**: 158. 1929.

The work is divided into three principal parts: biology, clinic and pathology of age. In the first part, the author discusses the physical chemistry of colloidal matter, the theory of protoplasmic hysteresis (Ruzicka) and the opinions of Lumiere. In the clinical part, the changes brought about by disturbances of internal secretions are discussed, first of all the genital glands, thyroid, adrenals, and hypophysis, which determine a new old age terrain, and on account of which in advanced years new symptoms of disease and even modifications of disease make their appearance. In advanced years hypothyroidism predominates, yet a decided myoedema is relatively seldom observed. The insufficiency of the parathyroids seldom leads to pronounced

tetany; as a rule, only an augmentation of the mechanical nervous irritability is observed. The influence of the parathyroid is often shown in the metabolism of calcium which often amounts to osteoporosis. The hypophyseal changes show themselves mostly in acromegaly which often occurs in older women. In senility, the hypofunction of the genital glands is of first importance, i.e. as hypofunction of the interstitial gland in males and of the corpus luteum in females. Whether the operations according to Steinach and Voronoff really have in whole sense of the word the effect of rejuvenation, whether they have the sense of a stimulant therapy, or whether there exists really a regeneration of the function of the internal secretion of the genital glands, has as yet not been indisputably proved. In the third part, which treats the pathology of age, diseases to which old age is most subject and which influence the general constitution of individuals, are discussed. To this category belong, first of all, atheroxerosis and atherosclerosis which are the cause of 52% of deaths. Disturbances of the vegetative nervous system and vasomotor cramps lead to dyspragia and Raynaud's disease, atheroma of the vessels leads to embolism and thrombosis, which in turn lead to senile gangrene. The weakness of the heart is the cause of gradual diminution of blood-pressure which gives rise to disturbances in the nourishment of various organs, viz., that of the central nervous system. Tuberculosis of the lungs often appears in old age and is the cause of 20% of deaths.—Author's Abst. Abbreviated.

Sexual influence of non-sexual endocrine glands. Virility action of the suprarenal and hypophysis substances (L'influence sexuelle des glandes endocrines non-génitales. L'action virilisante de la substance cortico-surrénale et de l'hypophyse). Marañon, G. Rev. franç. d'endocrinol. **8**: 1. 1930.

A review of the literature citing evidence that both glands are significant factors.—R. G. H.

Physiology of the corpus luteum. V. The preparation and some chemical properties of progestin, a hormone of the corpus luteum which produces progestational proliferation. Allen, W. M., Am. J. Physiol. **92**: 174. 1930.

An improved procedure for the preparation of a hormone of the corpus luteum which produces progestational proliferation is described, and evidence is presented to show that it is destroyed by alkalis, thus differentiating it chemically from oestrin. The purified product is not destroyed by mild acid hydrolysis nor is it associated with cholesterol color-reactions. It is relatively stable to heat and mild oxidation. Data are given regarding the yields of active substance. The oily preparations deteriorate rapidly but they may be kept in ethyl alcohol for long periods of time without loss. The name "progestin" is proposed for this specific hormone of the corpus luteum.
—Author's Summary.

Physiology of corpus luteum VII. Maintenance of pregnancy in rabbit after very early castration, by corpus luteum extracts. Allen, W. M. and G. W. Corner. Proc. Soc. Exper. Biol. & Med. **27**: 403. 1930.

Female rabbits were doubly ovariectomized 18 hours after mating. Corpus luteum extracts, prepared by the authors, were administered daily subcutaneously. In 4 animals pregnancy was maintained until full term and spontaneous delivery. In 2 animals fully developed dead foetuses were found on the 34th and 36th days.—M. O. L.

Hormone content of human ovarian tissues. Allen, E., J. P. Pratt, Q. U. Newell and L. J. Bland, Am. J. Physiol. **92**: 127. 1930.

Analyses of hormone content of isolated tissues of the human ovary have been made by injections of fresh follicular fluid and by implantation of fresh corpora lutea, of follicle walls and of cortical stroma free from macroscopic follicles. The use of graded amounts of ovarian tissues has made possible roughly quantitative analyses. The test used as a criterion of hormone activity was the full oestrous reaction of the ovariectomized rat as reflected in the cell content of the vagina. Therefore the hormone sought was that responsible for the genital growth reactions of the periods of oestrus in lower mammals and of the intermenstruum in primates. Three of the recent corpora lutea tested

corresponded to unfertilized ova recovered from the uterine tubes. The stages of development of these and other corpora has been checked by histological studies. High yields of this hormone have been obtained from recent corpora removed from the 13th to 17th days of the menstrual cycle. There is a considerable decrease in amount by the 20th to 22nd day. Corpora of the first third of gestation contain considerable amounts. Two full term corpora gave negative tests. This last result indicates definitely that toward the end of gestation the corpus luteum of woman does not share responsibility for the large amounts of this hormone in the placenta, blood and urine. Liquor folliculi and pieces of follicle wall (mostly granulosa cells) contained considerable amounts of this hormone. In most cases the specimens tested were diagnosed as to normality or atresia by study (in section) of the follicle wall or the contained ova. In two cases of long continued bleeding large yields of hormone were obtained from cystic follicles. In one case of amenorrhea, large amounts of fluid from cystic follicles returned negative tests. Cortical stroma without macroscopic follicles, taken from ovaries containing follicles or corpora in which hormone was demonstrated, gave negative tests. These results added to earlier data demonstrate that, as far as the secretion of this hormone is concerned, the human corpus luteum merely continues an activity which is primarily follicular. This hormone content of the human corpus is highest just after ovulation in the early stages of transition from follicle to corpus luteum and decreases before the onset of the next menses. Normal stroma tissue of the ovarian cortex shares little in this function. Removal of parts of ovaries most active in secretion of this hormone, either large follicles or recent corpora lutea,—when done during the intermenstruum, usually results in the appearance of menstruation within the next 48 hours. These observations substantiate earlier conclusions from experimental work in monkeys that menstruation is degenerative in significance and primarily due to decreased action of this ovarian hormone after it has induced a certain amount of growth in the uterus.—Authors' Summary.

Folliculin and periodicity of sexual cycle (Ciclo sexual periódico y foliculina). del Castillo, E. B., and C. J. Calatroni, Rev. Soc. argent. biol. **6:** 108. 1930.

Daily injections of 0.1-2 units of folliculin were made in rats during several months. A latent period, summation of effect, after discharge and tendency to periodicity more marked with time, were observed. In castrates in spite of continued injections periodic oestrus was observed. Ovary and corpus luteum are therefore not indispensable for periodicity of cycle. Uterus and vagina have a periodic activity, autonomous or governed by an unknown factor, which is made manifest by the presence of folliculin.—J. T. Lewis.

Clinical experiments with oestrin. Dodds, E. C. and J. D. Robertson, Lancet, **218:** 1390. 1930.

The results of treating 86 cases with an accurately standardized preparation of oestrin are described. The conditions investigated were amenorrhea, menopause symptoms, and attempts to produce premature labor. Out of the 86 cases treated only about 30 showed objective improvement, onset of menstruation, abatement of vasomotor and nervous symptoms, or induced labor. The authors discount general improvement as a psychological effect, but consider further investigation with larger doses desirable.—M. A. Reid.

Development of the gonads in man (Über die Entwicklung der Keimdrüsen des Menschen). Fischel, A., Ztschr. f. Anat. u. Entwcklngsg. **92:** 34. 1930.

Interstitial cells are first demonstrable in the 42 mm. stage and are of mesenchymal origin.—A. T. R.

Intersexuality or hermaphroditism in mammals (Intersexualität oder Hermaphroditismus bei Säugetieren). Krediet, G., Ztschr. f. Anat. u. Entwcklngsg. **91: 251.** 1929.

The author discusses the histology of the gonads in correlation with the sex characteristics of hermaphrodite mammals, particularly in the pig, goat and man.—A. T. R.

The relation of basal metabolism to gestation. Litzenberg, J. C. and J. B. Carey, Am. J. Obst. & Gynec. **17**: 550. 1929.

This study is concerned with women having a metabolic rate slightly below normal, and showing no other signs of myxedema. The material was derived from 2,500 consecutive determinations of the basal metabolic rate in all types of patients, of whom 758 had a rate of minus ten or lower. In 91 cases of sterility, 52 women had a metabolic rate below normal; 36% had abnormal menses. These 52 women were treated with thyroid extract upon the supposition that the low rate was due to thyroid influence. Following this treatment, 30% of them became pregnant, two aborted (treatment was discontinued after conception), while 15 of the same group had aborted one or more times before treatment. Of a group of 137 women with lowered metabolism, 45% were sterile. There is a definite relation between metabolism and reproductive function. Lowered metabolism interferes with the function of reproduction in a large percentage of cases.—J. C. Litzenberg.

Action of predigested corpus luteum on excised vas deferens. Macht, D. I., A. E. Stickels and H. P. Leach, Proc. Soc. Exper. Biol. & Med. **27**: 152. 1930.

The most vigorous digestion of corpus luteum substance with pepsin or with pancreatin and bile did not decrease the potency of extracts of these corpora to cause contraction of the vas deferens.—M. O. L.

Concerning the different hormones and tissue respirations. III. Concerning castration and tissue respiration (Ueber die verschiedenen Hormone und die Gewebsatmung. III. Ueber die Kastration und die Gewebsatmung). Maeda, M., Folia Endocrinol. Japon. **5**: 101. 1930.

The author studied the influence of castration upon the tissue respiration of adult rabbits by means of Barcroft's manometer according to Warburg's method 2 or 3 months after castration. In male castrated animals the oxygen consumption is increased in the thyroid and decreased in the adrenals and pancreas, while the oxygen consumption of the spleen shows no change. The oxygen consumption of castrated female animals is increased in the thyroid and to a lesser degree in the adrenals. In the pancreas and spleen the respiration is unchanged. In the liver of castrated animals of both sexes the oxygen consumption remains practically unchanged, while the CO_2 production increases.—J. Gagnon.

The chemistry of oestrin. III. An improved method of preparation and the isolation of active crystalline material. Marrian, G. F., Biochem. J. **24**: 435. 1930.

By acidification and ether-extraction of urine from pregnant women, yields of oestrin varying from 8000 to 40,000 mouse units per liter can be obtained. Methods described by which these extracts can be greatly purified with a loss of only 40% of the activity throughout the process. This loss occurs entirely in the initial stage of saponification. The mouse unit of these purified preparations is of the order of 0.0006 mgm. From such purified preparations an active crystalline substance has been isolated. The mouse unit of this substance is about 0.00011 mgm. The possible identity of this substance with the active substances recently isolated by Butenandt and by Laqueur, Dingemanse and Kober is discussed. There is no proof at present that this substance is actually the pure hormone.—Author's Summary.

The relative amounts of oestrin required to produce the various phenomena of oestrus. Marrian, G. F. and A. S. Parkes, J. Physiol. **39**: 272. 1930.

The effective dose for the mouse is 200 units. On this basis 400,000 units would be required for the average woman which is much larger than is ordinarily given clinically.—C. I. R.

Physiologic effects of non-living testis grafts. Moore, C. R., J. A. M. A. **94**: 1913. 1930.

The author reports on 3 experiments and concludes that the spermatozoon motility test provides a means of revealing the presence of testis hormone in guinea pigs for periods as short as 10 days; yet by means of this test it has

been impossible to detect any hormone liberated from two autoplastic, whole testis grafts placed in subcutaneous pockets. In the rat a cytologic study of the prostate gland and seminal vesicles affords dependable methods of detecting the absence of hormone for periods of from 3 to 5 days. Here, also, two autoplastic, whole testis grafts in subcutaneous pockets fail to delay the onset of castration changes for as short a period as 2 days. The autolysis of nonviable testicular grafts does not liberate hormone in amounts that can be detected by any means at present known. Furthermore, the testis hormone is not stored within the body but is excreted by the kidneys. A continuous supply is necessary to maintain the secondary sex characters in a normal condition. There is no known acceptable evidence that nonviable testis grafts, i. e., grafts that fail to become incorporated within the body and actively secrete, exert any immediate or remote beneficial effect on the host organism.

Cholesterol in blood and bile during and after delivery and cholesterol in foetal blood (La colesterina sanguinea y biliar durante el embarazo y puerperio. Colesterinemia fetal). Palacios Costa, N. and M. V. Falsia, Rev. Soc. argent. de biol. **6**: 99. 1930.

Blood cholesterol was found to be increased in 30 pregnant women (0.262% average); during labor a further increase occurred; on the seventh day after delivery it had fallen to 0.172%. Blood serum from the umbilical cord had an average of 0.108%, no relation being found with the amount in the mother's blood. Bile cholesterol was 0.121%. When blood cholesterol was above 0.3% there was a corresponding increase in the bile cholesterol.

—J. T. Lewis.

Causes of Parturition (Investigaciones sobre la causa del parto). Perez, M. L., Rev. Soc. argent. biol. **6**: 75. 1930.

Transfusion of citrated blood of women in labour to women in the last stage of pregnancy produces symptoms of labour and delivery in 60%.

—J. T. Lewis.

Adsorption of the ovarian hormone from urine. Wiles, H. O., Proc. Soc. Exper. Biol. & Med. **27**: 125. 1929.

Ovarian hormone may be adsorbed quantitatively from urine by calcium phosphate.—M. O. L.

Source of the pigmentary hormone of the amphibian hypophysis. Allen, B. M., Proc. Soc. Exper. Biol. & Med. **27**: 504. 1930.

Unmixed pars intermedia of frog hypophysis transplanted into normal or hypophysectomized tadpoles becomes functional and causes maximal expansion of the superficial melanophores and deposition of pigment in the epidermal cells. Transplants of pure pars nervosa tissue do not cause pigmentary effects, while pars anterior tissue causes only a slight transitory effect.

—M. O. L.

Potent, sterile and low-protein extracts of the growth hormone from the anterior hypophysis. Evans, H. M., R. E. Cornish and Miriam E. Simpson, Proc. Soc. Exper. Biol. & Med. **27**: 101. 1929.

Procedures are given for the preparation of a sterile, low-protein extract of anterior lobe which caused marked increases in body weight of adult female rats when injected daily intraperitoneally. The anterior lobes had been stored for 18-24 months with solid CO_2. During the preparation of the extract, the temperature was never above 10°C. About 15 liters of extract was obtained from 2,000 grams of anterior lobes. The total solid content of the extract was about 1.1%.—M. O. L.

Anterior lobe of the pig and the monkey ovary. Hartman, C. G., Proc. Soc. Exper. Biol. & Med. **27**: 338. 1930.

An adult female rhesus was found to have a small uterus and minimal sized ovaries. Implantations of two anterior lobes from adult castrated pigs were given for 4 days. Nine days later at a laparotomy the uterus was found to be much enlarged and the ovaries were of relatively enormous size, with the entire surface studded with graafian follicles.—M. O. L.

Hypophysectomy and pancreatic diabetes in toads (Hipofisectomía y diabetes pancreática en el sapo). Houssay, B. A. and A. Biassotti, Rev. Soc. argent. biol. **6**: 8. 1930.

Further studies in 1200 Bufo arenarum showed that pancreatectomy is followed by diabetes with hyperglycemia and glycosuria. Simultaneous removal of the pituitary and the pancreas is not followed by glycosuria, and hyperglycemia is not constant and never very marked. Extirpation of the pancreas and the glandular lobe of the pituitary is followed by the same effects. If pancreatectomy and hypophysectomy are followed by daily implantations of anterior lobe, intense diabetes with hyperglycemia and glycosuria ensues. Lesion of the tuber cinerum prevents, in nearly all cases, pancreatic diabetes. If implantations of glandular lobe are made it appears as usual. The neuro-intermediate lobe has a similar but less marked effect. No other tissue of the toad is active in this respect. Therefore the glandular (anterior) lobe of the pituitary is an important factor in the production of pancreatic diabetes in the toad.—J. T. Lewis.

Sexual functions, pituitary and diencephalon in toads (Funcion sexual, hipófisis e hipotalamo en el sapo). Houssay, B. A. and L. Giusti, Rev. Soc. argent. de biol. **6**: 146. 1930.

Implantation of anterior lobe produces an increase in the volume and activity of testicles and subsequently increased sexual flexion reflex (not observed in castrates). Testicular implantation does not produce such effects. Injection of large doses of testicular extracts produces flexion reflex in castrates. Cauterization of infundibulum produces intense flexion reflex even in castrates and after hypophysectomy. This last operation also produces ovulation and expulsion of ova which is not observed after extirpation of the pituitary or of only the glandular lobe. Hypophysectomy or extirpation of glandular lobe when complete did not produce ovulation (rectifying previous communications). Pituitary of Bufo arenarum, B. d'Orbigny and L. ocellatus are active for these species. Alkaline extracts of mammalian pituitary, exceptionally produce incomplete ovulation in toads.—J. T. Lewis.

Tumors of the hypophysis, especially of the hypophyseal region and the midbrain (Geschwülste der Hypophyse, bzw. der Hypophysergegend und die Zwischenhirns). Illig, W., Virchow's Arch. f. path. Anat. **270**: 549. 1928.

Four cases are reported in which tumours were found in or about the pituitary. In a male aged 76 who died suddenly an eosinophilic adenoma was found in the pars anterior. The pituitary weighed 2.9 gms. (normal 0.6 gms.). There was no history of pituitary symptoms. A male aged 14 complaining of paralysis of the right abducens nerve and of right exophthalmos showed pronounced displacement of the pituitary by a sarcoma invading the skull. The third case, a male aged 46 with a history of right sided loss of hair for 8 years showed improvement on x-ray treatment but dystrophia adiposogenitalis gradually developed in the following 6 years. Pathological investigation disclosed a chief cell adenoma of the pituitary and regression changes about the ventricles. A female aged 45 who complained of headache, emaciation and disturbed speech and vision, on post mortem examination disclosed a chief cell adenoma of the pituitary, a cortical adenoma of the adrenal, acute cystitis and degeneration in the ganglion cells about the ventricles (hypophyseal cachexia). The writer concludes that the symptoms of pituitary disorder are still obscure and that the pathology of dystrophia adiposogenitalis and of hypophyseal cachexia remains in doubt. Clinical and pathological details of the 4 cases are supplied and fully discussed.—W. Susman.

Influence of extracts of hypophysis on the body weight, weight of fat, of sexual organs and of endocrine organs of rats. Korenchevsky, V., Biochem. J. **24**: 383. 1930.

An alkaline glycerol extract of fresh anterior lobe when injected into rats caused no marked increase in body growth, but did decrease intra-abdominal fat, and caused a decrease in the weight of the penis, prostate, seminal vesicles, testes and thyroids.—M. O. L.

Influence of extracts of hypophysis on nitrogen metabolism. Korenchevsky, V., and M. H. Dennison, Biochem. J. **23**: 868. 1929.

The oral administration of dried anterior or posterior lobe substance had no significant effect on urine flow or nitrogen metabolism in rats and rabbits. The subcutaneous injection of glycerol-water extracts of fresh anterior lobe produced on the day of the injection a decreased urinary flow and a decrease of 27% in the nitrogen metabolism. On the following day the nitrogen excretion remained depressed in rabbits, but increased above the normal in rats; urine volume was considerably increased.—M. O. L.

Oral administration of anterior pituitary tablets and our laboratory preparations on compensatory hypertrophy of thyroid gland. Loeb, L. and W. J. Siebert, Proc. Soc. Exper. Biol. & Med. **27**: 495. 1930.

Compensatory hypertrophy of the remnant of thyroid gland in guinea pigs, after the removal of one lobe and ½ to ⅔ of the other, was much diminished or entirely prevented by feeding daily a tablet of Armour's anterior pituitary substance. The feeding of anterior lobe substance prepared in Loeb's laboratory did not prevent the normal compensatory hypertrophy or diminished it only slightly. Fifty-four guinea pigs were used.—M. O. L.

The hypophysis in old age (L'hypophyse chez le vieillard). Lucien, M., Rev. franç. d'endocrinol. **6**: 441. 1929. Abst., Arch. Neurol. & Psychiat. **24**: 170. 1930.

After making a series of studies of the hypophysis in the aged, Lucien draws certain conclusions. He does not believe that one should speak of senile atrophy of the hypophysis, since in the anatomic study of the gland there is no evidence that there is reduction in its size or weight during the process of ageing. On the other hand, it is of note that the largest and heaviest pituitary glands have been found in old people. Microscopic study reveals areas which might be described as sclerosis, areas which are localized especially in certain parts of the gland, for example, at the hilus and near vascular pedicles, do not take on a different staining reaction and therefore should not be the cause of atrophy of glandular elements. He considers that the glandular parenchyma does not seem definitely reduced. The author expresses the opinion that histologic changes observed are evidence of a special functional state, which is peculiar to the hypophysis of old age. He calls attention to the fact that changes in the gland noted in old age have certain characteristics in common with changes occurring in some chronic nervous disturbances, such as chronic encephalitis and dementia paralytica. In the latter, there is evidence, besides a sclerosis, of a tendency toward enlargement of the acidophil cells. He considers, therefore, that the changes seen in the hypophysis of old age seem to be partly the result of an inflammatory process. This theory presupposes a new functional state of the hypophysis in the decline of life which is characterized by the accumulation of colloid substance in the lobes of the gland where pseudo-acinous forms are numerous; by the development of colloid vesicles around the hilus, and by the presence of a considerable amount of colloid in the pars nervosa. Thus, it would seem that there is in the hypophysis of the aged a true retention of colloid substance in the different parts of the gland. Secretory phenomena are in general slowed up, the acidophil elements being the only parts of the gland which preserve evidence of true glandular activity. The invasion of the posterior lobe by the basophilic cells of the pars intermedia is a contradiction of the hypothesis of slowing up of secretory phenomena. The migration of the acidophils into the pars nervosa would seem to indicate an active multiplication of these elements. The author interprets it in a different fashion. In normal functions of the hypophysis, cells of the pars intermedia emigrate to the pars nervosa where they slowly disappear by granular necrobiosis. The enigmatic bodies of Soyer represent these elements in the process of disintegration, and a collection of colloid in the neuro-hypophysis should be considered the result of this cellular piling up. This theory has been verified from experimental observations on the hypophysis of the cat. In the aged, emigrating cells, of the type found in the pars intermedia, progress little by little to the pars nervosa where their degeneration later shows itself. There is a slowing up of the cellulolytic processes and an accumulation of

basophilic cells in the neuro-hypophysis. Changes shown in the hypophysis of the aged may be an expression of a general slowing up of secretory function and a marked reduction of excretory function, of which the collected colloid is the most characteristic manifestation.

Effect of oestrin on gonad stimulating power of the hypophysis. Meyer, R. K., S. L. Leonard, F. L. Hisaw and S. J. Martin, Proc. Soc. Exper. Biol. & Med. **27**: 702. 1930.

Thirty-four immature female rats were given 2 r. u. per day of oestrous hormone for 30 to 70 days. Their pituitaries were then implanted into female rats 20 to 30 days old. The vaginas of these rats opened 9 to 25 days after the implantations, as compared with 4 to 5 days in similar rats receiving pituitary implants from controls which had not been injected with oestrous hormone. In further experiments male and female adult rats were castrated, and some of each sex were injected daily with 4 r. u. of oestrous hormone for 31 days. Their pituitaries were than implanted into immature female rats. The vaginas of the control and experimental recipients opened at about the same time but the ovaries of the experimental recipients weighed considerably less than the ovaries of the control recipients. The difference averaged 28% less for the male donors and 35% less for the female donors. The authors believe that the oestrous hormone inhibits the normal development of the ovary and decreases the gonad stimulating power of the hypophysis, and that the hypophysis of the female is more susceptible than that of the male.—M. O. L.

The relation of diabetes insipidus to the posterior pituitary and the tuber cinereum (Uber die Beziehungen des Diabetes Insipidus zum Hypophysenhinterlappen und zum Tuber cinereum). Sato, T., Arch. f. exper. Path. u. Pharmakol. **131**: 45. 1928.

Hypophysectomy of dogs was followed by a temporary or lasting polyurea in some but not in all cases. During the first week following successful hypophysectomy the amount of the oxytocic substance of the cerebrospinal fluid was below normal. After that period it became equal to that of normal cerebrospinal fluid. Extracts of the tuber cinereum of normal dogs contain a relatively small amount of oxytocic and of antidiuretic substance. Eight days after hypophysectomy they have a relatively high content of both. The theory is advanced that diabetes insipidus is produced by a deficiency in the antidiuretic substance of the posterior lobe extract and that whether or not it appears after hypophysectomy depends on whether or not the tuber cinereum is also destroyed.—Helen Bourquin.

Effect of various anterior pituitary preparations on basal metabolism in guinea pigs. Siebert, W. J. and R. S. Smith, Proc. Soc. Exper. Biol. & Med. **27**: 622. 1930.

Daily subcutaneous injections of either acid or alkaline extracts of beef anterior lobe caused in guinea pigs a marked and rapid rise in basal metabolism, which reached a maximum of approximately +60% within the first 10 days. Then the basal metabolism gradually returned to a level approximately 15% higher than the average found in normal guinea pigs. Feeding daily one 5 grain Armour anterior pituitary tablet to a guinea pig caused a gradual steady rise in basal metabolism which reached a maximum of approximately +60% in about 30 days. Feeding daily 5 grain pills of dried anterior pituitary substance prepared in Loeb's laboratory caused a slight gradual rise in basal metabolism which reached its maximum of approximately +25% in about 20 days, after which there was a gradual return to almost the normal level. Daily subcutaneous inoculations of fresh guinea pig anterior pituitary gland tissue caused a very slight gradual rise in basal metabolism which reached a maximum of approximately +15% in about 5 days, after which there was a decline.—M. O. L.

Biedl's disease (Biedlsche Krankheit). Ssereissky, M., Med. Klin. **25**: 1620. 1929.

The author states that as cases of Biedl's disease occur isolated and the number of cases cited in the literature up to the time of the present case is scarcely above 30, it is imperative that such cases be reported. His case (fe-

male, single, 27 years) presents the following syndrome: adiposity, pigment retinitis, polydactylism, deformation of the cranium with a high grade of mental retardation and imbecility bordering on idiocy. Symptoms of hypogenitalism are absent and in this respect the case is similar to that reported by Curschmann and Deusch. Onset of the disease was in early childhood and was marked by its slight progress. The change in the sella turcica distinguishes it from those of Biedl. Ratner considers this change a stigma of "diencephalic insufficiency." The fact that this patient was born in asphyxia and forceps were used merits consideration. There are two noteworthy facts which deserve especial attention: (1) Speech was slow in developing—patient first began to speak when 4 years old—and diction was only slightly altered; (2) Heredity—the presence of a pigment retinitis as a recessive indication and the polydactylism as a dominant sign in the clinical picture point to the rôle of hereditary factors. There is marked resemblance to the amaurotic idiocy and especially to the mutation form. The reference of authorities to hypophyseal-intermediary insufficiency in amaurotic idiocy and the hereditary nature of this disease justifies the attempt to place the Biedl syndrome in the heredo-degeneration group to which amaurotic idiocy belongs.—H. G. Beck.

What are the effects of roentgen ray irradiation of the pituitary gland in the treatment of the disorders of the menopause? (Was leistet die Roentgenbestrahlung der Hypophyse bei Behandlung klimakterischer Beschwerden?) Steinhard, B., Klin. Wchnschr. **8**: 1717. 1929. Abst., Arch. Physical Therapy, **11**: 250. 1930.

The author terms the results of x-raying the pituitary gland in climacteric disorders excellent. The favorable effect in climacteric disorders after roentgen castration is especially to be stressed. Technique: both temporal fields were given in one exposure ½ of the skin unit dose each. Also in favorably reacting cases the first irradiation only achieves an improvement of mostly about from 4 to 8 weeks' duration; after a second series the success mostly lasts for from about 4 to 5 months; a permanent success is in the majority of cases only to be obtained after the third or fourth series. Treatment should therefore not be discontinued prematurely. Vasomotor symptoms as hot flashes, outbreaks of sweat, headache, vertigoes are for the most part favorably influenced, which statement, however, cannot be advanced in regard to arthralgias of the menopause. The author points out, finally, that ovarian hormone therapy and bleeding, too, failed in those few cases, in which irradiation had also failed.

Simmond's disease (Über die Simmondasche Krankheit). Subotitza, K. H., Klin. Wchnschr. **7**: 944. 1928.

Simmond's disease is a chronic disease of the anterior pituitary and its early symptoms are loss of appetite and the falling out of the teeth. Achlorhydria follows and later the skin has an alabaster appearance. Anaemia, adynamia and cachexia are frequently present. Under präphyson administration (extract of anterior pituitary) rapid improvement follows. A female of 53 suffering from gastric symptoms, glaucoma, general weakness, emaciation, loss of hair and teeth, mental dullness, eosinophilia, subnormal blood sugar and a tolerance for insulin was first diagnosed as a case of myxoedema. New growth, pernicious anaemia and intestinal parasites were excluded. After thyroid treatment the response was slight and further investigation resulted in the diagnosis of Simmond's disease. Under präphyson the improvement was very pronounced. The action of präphyson is discussed as to its effect on the individual symptoms and as to the route by which it acts. So also are the symptomatology, differential diagnoses, and treatment of the disease considered.—W. Susman.

Effect of certain liver extracts on the blood sugar of diabetic patients. Blotner, H. and W. P. Murphy, J. A. M. A. **94**: 1811. 1930.

A study of the effect of the oral administration of certain liver extracts on the blood sugar of 23 diabetic patients indicates that they had a beneficial effect on the blood sugar of these patients. These extracts were prepared by making an aqueous extraction of calf's liver at from 35 to 40 C. at a pH of from 4.6 to 5.2 and then evaporating and precipitating this aqueous extract

at certain temperatures to varying degrees of dryness according to the method given in this paper. The average decrease in the blood sugar 8 hours after the control test meal in 18 out of 19 diabetic patients was 32.2 mgm.; the average decrease 8 hours following the test meal with the addition of the liver extract was 79.8 mgm. in these cases; while the average decrease in the 12 diabetic patients that were given the test meal and 10 units of insulin subcutaneously was 67.9 mgm. for the same period of time. Four patients with diabetes taking an aqueous extract have been observed with repeated fasting blood sugar determinations for 68 days, 29 days, 31 days and 5 months, respectively. In the first case the blood sugar remained at a lower level when the liver extract was taken, and then increased when it was omitted. In the second case the blood sugar was also at a lower level during liver extract therapy than previously, and when 7 units of insulin was injected subcutaneously twice a day the blood sugar level was slightly lower than during the period of liver extract therapy. In the third case the blood sugar level during liver extract therapy was at a slightly higher level than during the period when 13 units of insulin was taken. This may have been affected by the use of increased sedatives during this time. In the fourth case the blood sugar was stabilized by the liver extract, and the urinary sugar was decreased. These observations suggest that certain aqueous liver extracts contain a blood sugar reducing substance, active when taken by mouth, nontoxic and with an effect on the blood sugar concentration similar to that obtained with small doses of insulin, especially over a period of 8 hours.—Authors' Summary.

Secondary effects of insulin (Nebenwirkungen von Insulin). Bonem, P., München. med. Wchnschr. **76**: 1585. 1929.

A report is made of insulin anaphylaxis in three patients with idiosyncrasies, manifesting skin and mucous membrane rash and gastro-intestinal symptoms. In one case the author thinks that four years previously when the patient received insulin, she became sensitized so that when it was resumed the anaphylaxis occurred. Changing the make of insulin made no difference. Reactions here described occurred after ingestion of eggs.

Diabetic ketosis and functional renal insufficiency. Coburn, A. F., Am. J. M. Sc. **180**: 178. 1930.

The author divides his group of 122 instances of severe ketosis into 2 classes; 30 patients treated without insulin and 92 cases treated with insulin. Only two patients of the group treated without insulin recovered. In the cases treated with insulin diuresis was important if the coma was to disappear rapidly. The rapidity of the change from coma to health was directly proportional to the diuresis of acetone bodies. The intravenous infusion of hypertonic fluids containing glucose and alkali was the most efficient in causing excretion of acetone bodies. The author believes that excretion of acetone bodies is more important than their oxidation and also that development of anuria should be prevented.—E. L.

Relation of obesity and the tendency to the island organs (Beziehung von Mast und Fettsucht zum Inselorgan). Falta, W., Wien. klin. Wchnschr. **43**: 289. 1930.

Overinsulinization produces hypoglycemia, this in turn causes hunger, which is in turn followed by increased food intake and thus increase in weight. Increase in weight is not due altogether to the amount of food taken in, but to the amount which is metabolized and the oversurplus deposited as fat. Thus, it has been shown that patients on a constant diet, if given insulin, increase in weight up to a certain point at which they remain stationary. If the amount of insulin is increased, then the weight rises further and again becomes constant at this level. There is a limit to this, however, because when insulin is pushed above the limit, hypoglycemia occurs and with it the loss of weight. In insulin administration, even when the exogenous insulin is omitted often, the body weight keeps on increasing. This increase, heretofore, (in non-diabetics) could not have been brought about by the mere increase in diet, which speaks for the "training" of the islands to do more work. A review of the literature is given.—H. J. J.

The problem of pulmonary tuberculosis in patients with diabetes. Fitz, R., Am. J. M. Sc. **180**: 192. 1930.

Of the 1529 diabetic patients treated, 35 had pulmonary tuberculosis. The prognosis of these patients is not good, as 19 of these cases terminated fatally in one year or less. The patients should receive the best diabetic care and an adequate diet.—E. L.

A study of the relation of the blood sugar in plasma to that in the corpuscles in normal and diabetic individuals. John, H. J., J. Lab. & Clin. Med. **15**: 713. 1930.

The sugar content of the red blood corpuscles in the diabetic individual is strikingly lower than the sugar content of the surrounding plasma. As the amount of the sugar in the patient's blood increases, the increase occurs first in the plasma and does not appear until later in the red corpuscles. As the level of the plasma sugar falls, the corpuscular sugar as a rule keeps pace with it. Thus one rarely finds a higher sugar level in the corpuscles than in the plasma at the end of the glucose tolerance test, when the blood-sugar curve is descending. This relationship is not altered in severe cases of diabetes, that is, in cases in which the blood sugar is very high. In general, in the nondiabetic individual the corpuscles have a lower sugar content than the plasma, but this is not so marked as in the diabetic subject. In the normal subject, when the sugar in the plasma increases the corpuscular sugar rises more than it does in the case of a diabetic; but when the sugar curve is descending the corpuscles do not release their sugar so freely, and thus, as a general rule, one finds a higher level in the corpuscular sugar than in the plasma sugar at the end of the curve. A study of 1069 blood-sugar estimations shows that in nondiabetic individuals the ratio of the average increase of the sugar in the corpuscles, as compared with that in the plasma, to the average decrease was 17.12 to 12.20, while in diabetic individuals the corresponding ratio was 9.95 to 15.82. By suspending red corpuscles in 1000 mgm. per 100 cc. of glucose in a N/10 NaCl solution, the average increase of the corpuscular sugar after 2 hours was found to be 321% in corpuscles from nondiabetic individuals, and 185% in those from diabetic individuals. The washing of corpuscles in normal saline solution before their sugar content is estimated is contraindicated, as the sugar is washed out of the corpuscles and the estimations are therefore of no value. The present study would suggest that in diabetics the corpuscles have a lesser capacity to take in and to hold sugar than normally. Whether it is the decreased amount of insulin present or some other condition which is the dominant factor, future studies should disclose.—I. B.

Pancreatic tumors and insulin secretion (Tumeurs pancreatiques et secretion insulinique). Lemaire, A., Progrès. méd. **44**: 1205. 1929. Abst., Rev. franç. d'endocrinol. **8**: 70. 1930.

This is a case of Langerhan's tumor of the pancreas with hepatic metastases and hypoglycaemia. This observation proves again that cancers developing at the expense of a glandular tissue are endowed with a secretion the effects of which are practically identical with those of the normal secretion of the original tissue. To the group of endocrine tumors already known, of which the remarkable observation of von Eiselberg was the first, must now be added the Langerhansian adenomas and cancers. Hypoglycaemia by means of hyperinsulinism is the essential clinical interpretation of it.—Translated by J. Gagnon.

Atrophy of subcutaneous fat associated with insulin injections. Nichols, J. B., Am. J. M. Sc. **180**: 90. 1930.

Prolonged hypodermic administration of insulin sometimes causes atrophy of the subcutaneous fatty tissues in the vicinity of the injections. In this paper a case of the kind is reported and 34 other cases in the literature are reviewed.—Author's Summary.

Nondiabetic glycosurias. Rowe, A. W. and Mary McManus, Am. J. M. Sc. **179**: 761. 1930.

The etiologic background of a number of cases showing glycosuria but without demonstrable evidence of a diabetic condition has been studied. Certain non-endocrin states, including psychoses, lesions of the central nervous

system, primary anemia, lymphatic leukemia, malignant neoplasm, various types of hepatic dysfunction and syphilis, have shown a distinctive frequency of incidence of glycosuria. Further, certain of these conditions have appeared as complicating factors, in a group of patients with glycosuria whose primary complaint was not included in the list given above. Analysis of a similar series of disturbed endocrin functional states shows a similar incidence of glycosuria, even after those have been deleted which present the significant non-endocrin disorders as secondary complications. With but minor exception, all of the individuals show normal blood-sugar levels and the several group averages are entirely within conventional limits. The majority of the patients in the series show a depressed tolerance for galactose which is characteristic of the several conditions involved. Exception to the foregoing is noted in the case of thyroid failure, and far more strikingly in hypofunction of the pituitary, where increased galactose tolerance is occasionally associated with glycosuria. The same condition of glycosuria with normal blood sugar is noted in the physiologic state of pregnancy. It is concluded that the phenomenon of glycosuria is no more than one common end result of a wide variety of causes, many of which cannot be demonstrated to produce the effect through influence on or by the function of the pancreas. From this it is deduced that there are a number of factors concerned with the regulation of carbohydrate metabolism, of which the intrinsic function level of the islands of Langerhans, although most important, is but one.—Authors' Summary.

Studies on the circulation of the feet in diabetes mellitus with and without gangrene. Starr, I., Am. J. M. Sc. **180**: 149. 1930.

As gangrene of the feet has been attributed to decreased blood supply, the blood flow through the feet was determined in a small number of cases. The histamine reaction was usually determined in four areas of the lower extremity. Both the wheal and the flare produced were observed in over one hundred cases. The histamine reaction shows that the majority of diabetics have a subnormal circulation in the feet, 32% being normal, 34% somewhat impaired and 34% markedly impaired. This reaction also aids in choosing the level for amputation in cases of gangrene.—E. L.

Serum calcium and phosphorus of guinea pigs after administration of single and repeated doses of parathormone. Bodansky, A., J. E. Blair and H. L. Jaffe, Proc. Soc. Exper. Biol. & Med. **27**: 708. 1930.

In guinea pigs large doses (10 to 20 units per 100 gms.) of parathormone caused the serum calcium to rise to a maximum of about 16.0 mgm. about 24 hours after injection. Starvation did not intensify the effect in adult animals but did so in young pigs and also prolonged the effect. The serum phosphorus was modified in the same way, in general, although starvation of the adults intensified the effects somewhat. In doses as large as 30 units per 100 gms. given daily for several days, the serum calcium rose to 20 mgm. and serum phosphorus also rose to a high value. Doses less than 5 units per 100 gms. per day for 10 and 16 days had no apparent effects on serum calcium or phosphorus, but histological examination showed bone resorption, indicating mobilization and excretion of bone calcium in the absence of hypercalcemia.
—M. O. L.

Blood phosphorous and serum calcium in parathyroid deficiency. Esau, J. N. and O. O. Stoland, Am. J. Physiol. **92**: 1. 1930.

The average of 261 determinations on 71 normal dogs showed the following concentrations: calcium 10.84 (mgm. per 100 cc. serum), inorganic P. 4.44, total acid soluble P 26.65 (in mgm. per 100 cc. of whole blood), inorganic P/Ca ratio 0.41, and total acid soluble P/Ca ratio 2.42. Although the phosphorus compounds, particularly of the skeletal muscles, may play a leading rôle in the symptomatology and death of parathyroid deficient dogs, the inorganic and total acid soluble phosphorus changes of the whole blood are not primarily etiological. In thyroparathyroidectomized dogs the inorganic P always increases, but the total acid soluble P tends to increase with the severity of the symptoms manifested. However, if the symptoms of parathyroid deficiency are mild and delayed in onset for 3 or more days there is usually a fall to below the normal. A low blood inorganic P and particularly a low total acid soluble P is highly favorable to recovery from parathyroid deficiency. The beneficial effects of magnesium lactate and morphine sulphate

despite a secondary progressive rise in inorganic P and total acid soluble P are attributed to their depressant action on the respiratory center and other nervous structures. The rate of calcium fall, and not so much its absolute concentration in the serum, is related to the onset of parathyroid deficient symptoms but seems to bear no relationship to the type and severity of symptoms initially manifested. As a rule both P/Ca ratios largely varied opposite to the calcium change and at the time of death or when symptoms of parathyroid deficiency appeared were increased by 90 to 300% (inorganic P/Ca) and 60 to 150% (T.A.S.P/Ca) above the normal. Two out of 12 thyroparathyroidectomized dogs, none of which were treated, made a complete recovery though the blood picture and clinical symptoms were identical to those that died of parathyroid deficiency (high inorganic P and T.A.S.P. and low serum calcium accompanied by mild tetany and severe depression). It is concluded that the behavior of the calcium and acid soluble phosphorus compounds in the blood of dogs suffering from parathyroid deficiency is largely due to a disturbance of phosphocreatin metabolism within the muscle fiber (and perhaps other tissues) which greatly involves the Ca/K ratio, thereby affecting also the permeability and irritability of tissues whereby metabolites otherwise non-toxic occur in excess and gain access to the cellular protoplasm which results in the various clinical manifestations found in parathyroid deficiency. The marked increase of the blood P compounds in early and severe parathyroid deficiency and parathormone over-dosage is attributed to the increased destruction of tissue proteins and a terminal retention.—Authors' Summary.

Parathyroids and fluoride hypocalcemia (Paratiroides e hipocalcemia fluórica). Gerschman, Rebeca, Rev. Soc. argent. biol. **6**: 25. 1930.

Intravenous injection of sodium fluoride (30 mgm. per kgm.) in dogs produces a maximum lowering of calcemia in two hours (3.3 mgm. % average) with a gradual rise from the third hour. Parathyroidectomized dogs did not show the secondary rise.—J. T. Lewis.

Parathyroids and hypercalcemia (Paratiroides y curva hipercalcémica). Gerschman, Rebeca, Rev. Soc. argent. biol. **6**: 35. 1930.

Blood calcium curves following $CaCl_2$ injection are identical in (1) normal, (2) recently parathyroidectomized dogs and (3) animals operated on the previous day, except that the descending curve is somewhat more rapid in (2) and slower in (3).—J. T. Lewis.

The function of the parathyroids in the light of the pathological physiology of the organ (Die Funktion der Epithelkörperchen im Lichte der pathologischen Physiologie des Organs). Gold, E., Klin. Wchnschr. **8**: 2247. 1929.

Preceding physiological work has established the function of the parathyroid hormone as the maintenance of the levels of serum calcium and phosphorus and of the rate of excretion of calcium. Tetany has been identified as due to a failure of this function. Erdheim recognized the frequency of parathyroid enlargement in osteitis fibrosa cystica and osteomalacia and attributed the change to compensatory hyperplasia. Mandl (1925) and Gold (1927) removed parathyroid tumors in patients with osteitis fibrosa cystica and observed a marked clinical improvement together with a decline of the high blood calcium and an abatement of the urinary calcium loss. A summary of the confirming authors is given. Osteitis fibrosa cystica is therefore hyperparathyroidism in opposition to tetany, which is hypoparathyroidism. Withdrawal of bone deposits through long continued injections of parathyroid extract is demonstrable experimentally. Careful studies of calcium and phosphorus relationships should now be made on such other conditions as myasthenia gravis and paralysis agitans which have been held to be of parathyroid origin.—Allan T. Kenyon.

Parathyroid hormone and calcium metabolism (Studien über das Epithelkörperchenhormon und den Kalkstoffwechsel). Inaba, M., J. Biochem. **12**: 35. 1930.

Oral administration of parathyrenin to rabbits had no effect on the blood calcium (Kramer and Tisdall method). Subcutaneous administration (0.8-1.0 cc. per kilo) produced a transitory hypercalcemia: intravenous injection

(0.2-0.3 cc. per kilo) produced a hypercalcemia of about 24 hours duration. Simultaneous injection of 1% $CaCl_2$ solution (5 cc. per kilo) increased the duration of the hypercalcemia to 140-166 hours. Calcium chloride alone caused only a 20-28 hour hypercalcemia. Atropin and pituglandol, injected with calcium chloride solution, increased the duration of the hypercalcemia, but not as definitely as parathyrenin. The increased blood calcium level was accompanied by a nearly parallel change in blood phosphorus (inorganic—Bell and Doisy method) and by increased excretion of calcium in urine and feces. —B. S. Walker.

Production in guinea pigs of fibrous bone lesions with parathyroid extract. Jaffe, H. L., A. Bodansky and J. E. Blair, Proc. Soc. Exper. Biol. & Med. **27**: 710. 1930.

In guinea pigs subcutaneous injections of parathormone regularly produced the bone changes typical of ostitis fibrosa, including the appearance of new bone a few days after cessation of the treatment.—M. O. L.

The effect of vitamin D and of reaction of diet upon response to parathyroid extract. Morgan, A. F. and E. A. Garrison, J. Biol. Chem. **85**: 687. 1930.

Experiments on 28 dogs, the majority of which had been kept on a known diet since weaning, indicate that vitamin D and alkaline reaction of diet, together or separately, increase the susceptibility to injection of parathyroid extract. Dogs reared on artificial diets (Ca: P ratio 1.18 to 1.64) without vitamin D, respond but little to parathyroid extract. Similar dogs, given vitamin D, show abnormally large increases in serum Ca and inorganic P, together with fatal symptoms of overdosage. Dogs given diets of normal Ca: P ratio, low in P and Ca, with or without vitamin D, respond with similar toxic symptoms to parathyroid extract, if sufficient sodium carbonate is given to make the urine alkaline. Administration of ammonium chloride has little effect on the response to parathyroid administration.—B. S. Walker.

The relief of parathyroid tetany by injections of uranium nitrate. Swingle, W. W., Physiol. Zoöl. **1**: 496. 1928. Abst. Biol. Absts. **3**: 1207. 1929.

Recent studies have shown that slight changes in the acid-base equilibrium, with a shift in the reaction of the blood toward the acid side, exert a profound effect upon the tetany of parathyroid insufficiency. Uranium nitrate is a powerful nephrotoxic agent, and when injected into a normal or parathyroidectomized dog produces a marked acid intoxication. The acidosis appears to be due to retention of phosphate and sulphate ions and probably also some organic acid. Parathyroidectomized dogs exhibiting violent tetany symptoms have a normal acid-base equilibrium. Following injection of uranium nitrate, the CO_2 capacity, CO_2 content, and pH of the blood drop, and accompanying the shift of the reaction of the blood to the acid side, the tetany symptoms disappear. The dog remains free from tetany for a week or ten days, plays about in normal fashion, and eats heartily. Tetany again supervenes when the acid-base equilibrium returns to normal. The serum Ca increases slightly following injection of uranium nitrate. The answer to the question why changing the reaction of the blood toward the acid side brings about cessation of tetany symptoms and small increases in the serum Ca is probably that the increased hydrogen-ion concentration renders the serum Ca (a certain fraction of it) more diffusible and also takes care of any excess of P which may be present by stimulating its excretion.

Influencing callus formation in bone fractures (Experimentelle Beeinflussung der Callusbildung bei Knochenfrakturen). Glassner, K. and J. Haas, Klin. Wchnschr. **7**: 1633. 1928.

Experiments in the literature in regard to the effects of the thymus on bone healing may be divided into two groups: (1) the effect of thymus extirpation; (2) the effect of injection or feeding of thymus extracts. The authors working with cats report that removal of the thymus leads to deficient callus formation. Also, that thymectomized cats injected with thymus extracts plus phosphorus show a more vigorous callus formation than control animals with fractures in which the thymus is intact. Applying these results to human material, they report that after osteotomy for bow legs, thymus extracts hastened callus formation.—H. L. Jaffe.

Incidence of goiter in Finnland and its relation to the iodine content of the water (Orientierende Untersuchung uber die Verbreitung des Kropfes in Finnland und über deren Zusammenhang mit dem Jodvorkommen im Wasser). Adlercreutz, E., Acta med. Scandinav. **69**: 1. 1928. II. The etiology of goiter (Die Ätiologie des Kropfes), ibid. 187.

This is a discourse on endemic, epidemic and sporadic goiter followed by an exposition of the findings on the goiter problem in Finnland. In southern and middle Finnland goiter incidence is quite high. Next in order of goiter incidence is the plateau-like sea-rich section. Elsewhere goiter incidence also is high, some communities being affected more than others. Goiter is frequently observed on the sea coast; more frequently, however, on the coasts of the Finnish Gulf; rather infrequently is goiter encountered in Lapland. The fact in general is that goiter occurs by preference in the sea-rich portion of the country. Whether goiter in Finnland can be regarded as endemic and if so to what endemic type it belongs cannot be conclusively stated. Goiter here is associated with a paucity of cretinism, a frequency of Basedowian symptoms, and occurs almost constantly in women. While generally an inverse ratio is found to exist between the iodine content of the water and goiter incidence, in some localities the reverse is true,—some localities with iodine-poor water present low goiter incidence and others with iodine-rich water present a high goiter incidence. The author suggests that etiological factors other than iodine content of the water, particularly dietary habits, must be considered. The iodine deficiency theory of goiter causation is by no means tenable; iodine deficiency may be indirectly, not directly, responsible.—I. B.

Thyrotoxicosis in elderly persons without signs of goiter. Freund, H. A. and W. B. Cooksey, J. A. M. A. **94**: 1891. 1930. Abst., A. M. A.

The authors report 5 cases and call attention to the fact that primary hyperthyroidism frequently occurs in elderly persons without visible or palpable goiter. These patients more often present symptoms referable to the gastro-intestinal tract as their initial complaint. The usual signs of exophthalmic goiter are generally obscure. Compound solution of iodine promptly controls and terminates the vomiting, which in one instance had persisted for four weeks without relief. Subtotal thyroidectomy is often necessary. Prolonged preliminary treatment, however, is essential to prepare these patients for operation. Their response to treatment is striking and progressive, materially improving their chances for recovery from operation. In the two cases that came to operation, intensive preliminary treatment did not prove adequate. In three cases the continued use of iodine solution with only slight periods of interruption has succeeded in arresting the hyperthyroidism. Its prolonged administration in these cases has not produced ill effects. Its continued administration is apparently essential to maintain the patient's sense of well being.

Basedow's disease with unilateral symptoms (Morbo de Flajani-Basedow a sindrome unilateral). Boccia, D., Rev. sud-am. de endocrinol. **13**: 242. 1930.

A case history with extensive bibliography.—R. G. H.

The probable etiology of endemic goiter (Die Vermütlichen Ursachen des Gebirgskropfes). Grassl, München. med. Wchnschr. **76**: 1375. 1929.

This is a review of the theories of the etiology of endemic goiter. According to the author, the goiter question remains one of nutrition, and in general is involved in the general rules of food assimilation. Two factors are concerned herewith; that of motor energy and of chemical reaction. The sun's rays and the iodine plant life play vital rôles in this connection. Under normal circumstances these factors control functional equilibrium. Through disturbance of one or other of these factors there result disturbed vital stimuli with sequential marked changes in nutritional balance and endemic goiter formation.—I. B.

Masked hyperthyroidism. Hamburger, W. W. and M. W. Lev, J. A. M. A. **94**: 2050. 1930.

By the term masked hyperthyroidism is designated a group of middle aged, apathetic men and women patients, suffering with thyrotoxicosis, in whom the classic signs and symptoms of hyperthyroidism are wanting but who present

an atypical, clinical picture of some other type of diseases, as organic heart disease, congestive heart failure, angina pectoris, diabetes mellitus or pernicious vomiting. This group bears a certain relation to the cases of "maladie de Basedow, forme frustes" discussed in the literature. The diagnosis of masked hyperthyroidism, in addition to the points mentioned, rests on a suggestive increased warmth, redness or pigmentation of the skin; slight staring expression of the eyes, increased restlessness; unexplained loss of weight; persistent increase in the basal metabolic rate; improvement or relief of symptoms, and decrease in the basal metabolic rate following iodine medication and thyroidectomy and the histologic appearance of the removed glands. It is important that this frequently undiagnosed or misdiagnosed group of cases be recognized, in spite of the difficulties in diagnosis.—Authors' Summary.

Iodine and goiter (Jod und Kropf). Jansen-Bonn, W. H., München. med. Wchnsch. **75**: 645. 1928.

The iodine content of the blood and of thyroid structures speak rather against the iodine deficiency theory of goiter formation. The quantity of iodine content is no indication of the presence of a potent thyroid hormone nor does it indicate the quantity of the latter. The goiter problem must rest on the matter of the quality of the thyroid secretion and of this matter we know little. Many factors extrinsic to the iodine content play their part in thyroid disturbances, among which are the influence of soil, heredity, the vegetative nervous system, the rôle of the various other ductless glands, puberty, menstruation, pregnancy, and the menopause. The author sounds a timely warning against the indiscriminate use of iodine in goiter prophylaxis. —I. B.

Collateral blood supply to the thyroid gland (Über die kollaterale Blutversorgung der Schilddrüse). Kurkowsky, W., Ztschr. f. Anat. u. Entwcklngsg. **91**: 692. 1930.

An experimental study on dogs showing that unilateral or bilateral ligation of the thyroid arteries causes no change in the general appearance of the animal as a whole and no macroscopic or microscopic changes in the thyroid gland due to the establishment of collateral circulation mostly from arteries of adjacent muscles. Ligation of the thyroid veins produced no postoperative change in the gland for the same reason.—A. T. R.

Cytological changes in thyroid apparatus and spinal ganglia of rats treated with thallium. Ma, W. C. and J. W. Mu, Proc. Soc. Exper. Biol. & Med. **27**: 249. 1930.

The administration of 8 mgm. of thallium acetate per kilo of body weight to albino rats produced definite changes in the Golgi apparatus and mitochondria of the thyroid. One week after the injection the Golgi apparatus was changed from a network into droplets, and the mitochondria from filaments into segmented granules. In two and three weeks after injection the changes were still more marked, with a reduction in number of the elements and a further dispersion. The staining reaction of the colloid of the vesicles changed from basophilic to acidophilic. Four weeks after the injection recovery began which was complete two weeks later.—M. O. L.

Coexistence of myxedema and pernicious anemia. Means, J. H., Proc. Assoc. Am. Physicians, May 6-7, 1930. Abst., J. A. M. A. **95**: 74. 1930.

Myxedema and pernicious anemia have a superficial resemblance, and sometimes the diagnoses are confused. Paresthesia, anemia, edema, achlorhydria and mental changes are seen in both diseases. The two conditions sometimes coexist. This has been cited by several workers. In our studies we enumerated five cases in which both diseases were present. One patient, a woman, aged 73, for two years had had symptoms of paresthesia, sore tongue and yellow skin. She was considered to have pernicious anemia and received liver extract. She was given morphine for some reason, and this increased the myxedema so that she presented a terminal picture of myxedema. This phenomenon has been observed by Lund and Benedict. She was given thyroxin and greatly improved. After 50 days in the hospital the woman was well. Another patient, a man, aged 53, who had had myxedema seven years before,

was relieved by thyroid and remained well on thyroid. Two years later he developed a true clinical picture of pernicious anemia. He was put on liver treatment. Thyroid was omitted at this time and the metabolism went to —40 and he showed myxedematous changes. In three of our cases the pernicious anemia appeared first; in the others, myxedema was present first. The two may coexist and both may be cured by the appropriate treatment. The necessity of thyroid treatment should be kept in mind in any case of anemia.

Effect of thallium acetate on the basal metabolism of rats. Mu, J. W. and C. K. Hu, Proc. Soc. Exper. Biol. & Med. **27**: 251. 1930.

In four rats injected with thallium acetate in doses of 12 and 8 mgm. per kilo, there was a transitory but definite decrease in the basal metabolic rate. Since thallium acetate causes degenerational changes in the thyroid gland, the authors attribute the variations of the metabolic rate to an action of the thallium on the thyroid.—M. O. L.

Athyreosis with few symptoms, together with a consideration of the toxic action of irradiated ergosterol (Uber athyreose nebst einige Befunden, betreffend die Frage von der toxischen Wirkung des bestrahlten Ergosterins). Nikoloeff, N. M. and Z. W. Zimbler, Jahrb. f. Kinderh. **126**: 222. 1930.

Complete absence of the thyroid gland in a child of one year of age was not accompanied by any symptoms, according to the authors, of athyreosis or myxedema. A study of the case report, however, reveals some symptoms which may be placed upon a hypothyroid basis, such as underweight and undergrowth, saddle nose, edema of lids, thick lips, umbilical hernia, thickened tongue, large fontanelle, absence of teeth, and a dry, edematous skin. There were no myxedematous pads in the supraclavicular region. The child had always been a weakling from birth. Several chemical studies of the blood were made but the findings cannot be accepted as being due to the athyroid condition as the child had in addition a multiplicity of conditions such as bilateral otitis media suppurative, purulent meningitis, double pneumonia, noma, subacute entero-colitis and sepsis. Post mortem examination of the endocrine organs showed an atrophic state of the thymus, hypophysis, adrenal, pancreas and parathyroids. There were no evidences of hypertrophic compensatory processes in any endocrine glands. There was no apparent increase in thyroidin following the administration of irradiated ergosterol. The authors feel that some of the symptoms present could be attributed to the toxic action of the ergosterol in the light of a hypercalcemia.—M. B. G.

Interchange of ionized and biological iodine (Die Transformation von ionisiertem und biologischem Jod). Pfeiffer, G., Biochem. Ztschr. **215**: 197. 1929.

Two unilaterally thyroidectomized dogs were fed iodine, one in the form of KI, the other in iodized radish leaves. Comparative analyses were made of the extirpated half-gland, of urine and feces during the experiment, and of the residual thyroid tissue after the experiment. The dog fed with KI retained more iodine in the tissues as a whole, but the dog fed with the "biological" iodized material had a higher iodine concentration in the thyroid gland, with a greater absolute and relative increase in iodine content of the thyroid as compared with the initial analysis.—B. S. Walker.

Basal metabolism studies in normal pregnant women with normal and pathologic thyroid glands. Plass, E. D. and W. A. Yoakam, Am. J. Obstet. and Gynec. **18**: 556. 1929.

The basal metabolic rate shows an increase during normal uncomplicated pregnancy of approximately 15%, with a fall to normal in the first few days after delivery. A greater rise with slower fall to normal suggests increased thyroid activity incident to pregnancy. A small percentage of women with clinically normal thyroid glands have a metabolic rate which rises above plus 20%. Patients with palpable thyroid disease show a greater tendency toward such high rates, the incidence rising to 35% with small colloid and adenomatous goiters, and to 50% in the large colloid type. This is taken to indicate that pathologic thyroid glands are less able to respond normally to the demands of

gestation, but tend to function abnormally and so to produce symptoms of hyperthyroidism. Iodine, given prophylactically during pregnancy, is apparently unable uniformly to prevent gestational hypertrophy of the normal thyroid gland, but seems to be quite effective in preventing such a change in glands which are pathologically altered when pregnancy begins, and may actually lead to a reduction in the size of certain colloid goiters. Iodine given to pregnant women acts very effectively to prevent the appearance of congenital goiter in the newborn.—Authors' Summary.

A direct physiological demonstration of the existence of a thyroid hormone which regulates the excitability of the psycho motor centers (Demonstration physiologique directe de l'existence d'une hormone thyroidienne regulatrice de l'excitabilite des centres psycho-moteurs). Regnier, J., D. Santenois, P. Vare, H. Verdier and M. Vidacovitch. Rev. franç. d'endocrinol. **8**: 26. 1930.

Blood was collected from the thyroid veins of dogs and the serum injected into experimental animals. The chronaxie of the motor cortex (sygmoid gyrus) was determined by the Lapicque method before and after injection. The decreased chronaxie resulting is cited as direct evidence that the thyroid gland secretes a substance that causes increased irritability of the cerebral cortex. Significantly positive results were obtained, however, only in dogs that were "vagotonic," i. e., giving a strongly positive oculo-cardiac reflex. It is deduced, therefore, that the vagus nerve has a regulatory influence via the thyroid on cortical excitability. The deduction is confirmed by the effect of high section of the vagus which, by cutting off access to the thyroid, leads to decreased cortical excitability. Similarly, increased cortical excitability was shown to follow small doses of eserine or eletric stimulation of the vagus fibres to the thyroid; this is ascribed to hyperthyroidism thereby induced. Thyroidectomy was found to lessen and thyroid extract, to increase the cortical excitability. Under more favorable conditions of thyroid activity an exciting effect of carotid blood upon the cortex could be demonstrated.—R. G. H.

Cholesterol metabolism in relation to thyroid and spleen (Untersuchung über Cholesterinstoffwechsel in seiner Abhängigkeit von Schilddrüse and Milz). Sakai, H., Biochem. Ztschr. **216**: 32. 1929.

The average cholesterol content of the livers of three normal guinea pigs was 0.188%, of the suprarenals of five normal guinea pigs, 4.338%. Following thyroid feeding, three guinea pigs gave cholesterol percentages of 0.247 in the livers and 7.329 in the suprarenals (averages). The cholesterol was determined gravimetrically as the digitonid. Following removal of the spleen from fifteen guinea-pigs, variations above and below the normal range of cholesterol content of liver and suprarenals were observed, both in the normal group and in the thyroid-fed group.—B. S. Walker.

Thyroglobulin versus thyroxin. Schulhof, K., Am. J. Physiol. **93**: 170. 1930.

The presence of thyroglobulin in the lymph and blood from the thyroid gland has been established, while there is no evidence for the actual secretion of free thyroxin. It is possible that the latter is split off from the thyroglobulin in the blood or organs, but thryoglobulin may have other active groups than thyroxin. Injections of foreign thyroglobulin in rats have a marked action on the basal metabolic rate and on the weight. When injected in doses equivalent in their iodine content with thyroxin, the action of thyroglobulin is of the same order, at least within the quite large limits of the probable error of the methods used. Other methods which seem to be more promising are discussed.—Author's Summary.

The Arneth count in normal and in thyroidectomized sheep. Simpson, Ethel D., J. Exper. Physiol. **19**: 309. 1929.

There was a displacement of the Arneth count to the right which appeared two or three weeks after operation and persisted for three to four weeks.
—C. I. R.

The sedimentation rate of the erythrocytes as a diagnostic and therapeutic index in thyroid disturbances (Die Senkungsgeschwindigkeit der Erythrocyten als Diagnosticum und therapeutischer Masstab bei Schilddrusenerkrankungen). Taterka, H., and C. H. Goldmann, Klin. Wchnschr. 9: 303. 1930.

The sedimentation rate of the erythrocytes is a simple and reliable method of determining functional disturbances and results of treatment of thyroid disturbances, particularly Basedow's disease. The results of roentgenotherapy can be so determined, as can the results of attention to patients with hypothyroidism. In Basedow's disease a lessening of the rate of sedimentation runs parallel with a lessening of toxicity. In hypothyroidism there is a retardation of the rate of sedimentation as compared to normal. Iodine administration is likewise capable of varying the sedimentation rate.—I. B.